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Award Number: DAMD17-01-1-0447

TITLE: Quality of Life and Functional Status across the Life Course

PRINCIPAL INVESTIGATOR: Michelle J. Naughton, Ph.D.

CONTRACTING ORGANIZATION: Wake Forest University School of Medicine
                          Winston-Salem, NC 27104

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14. ABSTRACT
This Behavioral Center of Excellence in Breast Cancer contains three separate, but related research projects focused on breast cancer patients' quality of life and functional status. There is also a Biostatistic's Core Facility supporting all three studies. The three projects are: Project 1) Menstrual Cycle Maintenance and Quality of Life Following Treatment for Breast Cancer: A Prospective Study. This is a study of women aged 45 years and younger diagnosed with a first breast cancer. Project 2) Investigating Mechanisms to Explain Age Associated Differences in Quality of Life Among Breast Cancer Patients. This study examines psychosocial and clinical factors associated with patient's (aged 18-80+ years) coping and quality of life during the first 18 months post-diagnosis. Project 3) Research on Optimal Recovery Practices in Breast Cancer (RESTORE). This is a randomized exercise intervention trial with a lymphedema prevention program. Project 1 is a continuation of a study that was initiated in January of 1998. Projects 2 and 3 are new protocols, which will begin patient recruitment in the fall of 2002. All three studies have the potential to greatly improve the functional status and life quality of breast cancer patients during treatment and beyond.

15. SUBJECT TERMS
breast cancer, quality of life, lymphedema, exercise

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OVERVIEW OF CENTER ACTIVITIES

I.   Progress of the Center-Specific Projects and Biostatistic's Core Facility

Summaries of the activities and progress of the 3 research projects and the Biostatistic's Core Facility are included in the annual reports for each specific project and Core. (See Table of Contents.)

II.   Advisory Board Activities

No formal advisory board meetings were held during the past grant year.

III.   Post-Doctoral Fellows

Currently, this Center Grant supports 2 post-doctoral fellows: Dr. Stephanie Walsh and Dr. Deborah Farmer. These fellows have participated in a variety of training and professional activities described below.

Recruitment for one additional (and final) post-doctoral fellow is underway currently. Ads have been placed in the _American Journal of Public Health_, the _APA (American Psychological Association) Monitor_, and _Outlook_ – Publication of the Society of Behavioral Medicine (website only). Electronic versions of the advertisements were also posted on several oncology and/or quality of life list serves. It is projected that the successful applicant will begin the post-doctoral fellowship during the summer of 2005.

a. Summary of Activities of Dr. Stephanie Walsh (now Dr. Stephanie Burwell):

Dr. Stephanie Walsh began the post-doctoral fellowship in June of 2003. Her fellowship ended on July 15, 2005. She is now an Assistant Professor at the University of Georgia, Athens, Georgia in the Department of Child and Family Development.

During her post-doctoral fellowship, she completed the following activities:

Professional Memberships:
2003-2005	Cancer Control Program, WFUSM
2003-2004	Psychosocial Oncology Group, WFUSM
2002-Present	American Association for Marriage and Family Therapy, Clinical Member
2003-Present	Collaborative Family Healthcare Association
2003-Present	American Psychosocial Oncology Society
2005-Present	American Association for Marriage and Family Therapy, Approved Supervisor

Book Chapters

Lyness, KP, Walsh, SR, Sprenkle, DH. (2005). Clinical Trials in Marriage and Family Therapy Research. In D.H. Sprenkle & F.P. Piercy (Eds.). Research Methods in Family Therapy, second edition. NY: Guilford Press.

Peer-Reviewed Journal Articles

Brucker, PS, Faulkner, RA, Baptist J, Grames, H, Gulish, L., Walsh, SR, Willert, A. (2005). The Internship Training Experiences in Medical Family Therapy of Doctoral-Level Marriage and Family Therapy Students. The American Journal of Family Therapy, 33, 131-146.

Walsh, SR, Manuel, J, Avis, NE. (2005). The Impact of Breast Cancer on Younger Women's Relationships with their Partners and Children. Families, Systems, & Health, 23, 80-93.

Walsh, SR, Denton, WH. (2005). Clinical Issues in Treating Somatoform Disorders for Couple Therapists. The American Journal of Family Therapy, 33, 225-236.

Burwell, SR, Brucker, PS, Shields, CG. (In Press). Attachment behaviors and proximity-seeking in cancer patients and their partners. Journal of Couple and Relationship Therapy, 5(3).

Manuel, JC, Burwell, SR, Crawford, SL, Lawrence, RH, Farmer, DF, Hege, Phillips, K, Avis, NE. Younger Women's Perceptions of Coping with Breast Cancer: A Mixed Methods Approach. Cancer Research. (In press)

Burwell, SR, Case, D, Avis, NE. Sexual problems in Younger Women Following Breast Cancer Diagnosis. Journal of Clinical Oncology. (In press)

Under Review:

McWey, LM, Burwell, SR. (Revise and resubmit). The impact of an evidence-based pilot curriculum in a marriage and family therapy doctoral program: An exploratory study.

Burwell, SR, Denton, WH, Snively, BM. (Under review). Demand-Withdraw Communication in Somatoform Patients and their Partners.

Williams, J, Burwell SR, Foy, CG, Foy JM. (Under review). Addressing Behavioral Health Issues during Well Child Visits by Pediatric Residents.

Published Scientific Abstracts:

Walsh, SR, Case, D, Avis, NE. (2004). Changes in Sexual Functioning Following Diagnosis among Younger Women with Breast Cancer. Psycho-Oncology, 13 (1).

Walsh SR, Ip E, Petrek JA, <u>Naughton MJ</u>. Predictors of Depression in Younger Women with Breast Cancer During the First Two Years Post-Diagnosis. Proceedings of the 2005 Era of Hope: Department of Defense Breast Cancer Research Program Meeting, p. 487 (P69-7).

<u>Peer-Reviewed National Presentations</u>:

Walsh, SR, Brucker, PS. Open Forum: Post-Doctoral Fellowships. American Association for Marriage and Family Therapy Annual Conference, Atlanta, GA, September, 2004.

Denton, WH, Walsh, SR. Fundamentals of Making DSM-IV Diagnoses. American Association for Marriage and Family Therapy Annual Conference, Atlanta, GA, September, 2004.
Walsh, SR, Case, D, Avis, NE. Changes in Sexual Functioning Following Diagnosis among Younger Women with Breast Cancer. American Psychosocial Oncology Society (APOS), Orlando, FL, January, 2004.

Walsh, SR, Case, D, Avis, NE. Predictors of Sexual Function among Younger Cancer Survivors. Cancer Survivorship: Pathways to Health after Treatment, Washington DC, June, 2004.

Walsh, SR, Case, D, Avis, NE. Sexual Function in Younger Women with Breast Cancer. Poster presented at the Breast Cancer Center of Excellence Retreat. WFUHS, Winston-Salem, NC, January, 2004.

Walsh, SR, Ip, E, Naughton, MJ. Characteristics of Younger Breast Cancer Patients with Depressive Symptoms and Implications for Medical Family Therapy. The North Carolina Association for Marriage and Family Therapy, Cary, NC, March 2005.

Walsh SR, Ip E, Petrek JA, <u>Naughton MJ</u>. Predictors of Depression in Younger Women with Breast Cancer during the First Two Years Post-Diagnosis. Era of Hope: Department of Defense Breast Cancer Research Program Meeting. Philadelphia, Pennsylvania. June 11, 2005. (Presentation and poster)

Williams, J, Burwell SR, Foy, CG, Foy JM. Addressing Behavioral Health Issues during Well Child Visits by Pediatric Residents. SDBP Meeting, San Diego, CA, September 2005.

<u>Invited Presentations</u>:

Walsh, SR, McQuellon, R. The Healing Connection: Strengthening the Relationships of Cancer Patients and their Partners. Presented at Cancer Services, Incorporated, Winston-Salem, NC, April, 2004.

Walsh, SR. Sexual function among younger women with breast cancer. Presented at Cancer Services, Incorporated, Winston-Salem, NC, May, 2004.

Courses Audited:

Grant Writing
Medical Outcomes
Applied Linear Models
Stats I & II

Other:

Attended the UNC-Chapel Hill and Duke "Couples and Health" Research group monthly meetings Nov. 2004-March 2005.

Was nominated and applied for the AFTA (American Family Therapy Association) Early Career Membership in May 2005.

b. Summary of Activities of Dr. Deborah Farmer:

Dr. Deborah Farmer began the post-doctoral fellowship on September 1, 2003. Her fellowship ended on September 30, 2005. She is currently on the job market for a faculty position in cancer research, and is a Research Associate in the Division of Public Health Sciences and the Department of Neurology at the Wake Forest University School of Medicine.

The following is a summary of the activities that Dr. Farmer completed while on the DOD post-doctoral fellowship:

Published Journal Articles:

Foley KL, Farmer DF, Smith R, Petronis V, McGraw S, Smith K, Carver C, Avis NE. A qualitative exploration of the cancer experience among long-term survivors: Comparisons by cancer type, gender and age. *Psycho-Oncology* 2006;15(3):248-258.

Jones AS, Fowler TS, Farmer DF, Anderson RT, Richmond DW. Description and Evaluation of a Faith Community-Based IPV Pilot Program in Forsyth County, NC. *Journal of Religion and Abuse* 2006;7(4):55-87.

Farmer DF, Bell R, Stark N. Cancer screening among Native Americans in eastern North Carolina. *Journal of Health Care for the Poor and Underserved* 2005;16:634-642.

Foy CG, Bell RA, Farmer DF, Goff DC, Wagenknecht LE. Smoking is associated with increased incidence of diabetes among United States adults: Findings from the insulin resistance atherosclerosis study. *Diabetes Care* 2005;28(10):2501-2507.

Mihalko S, Brenes G, Farmer DF, Katula J, Balkrishnan R, Bowen D. Challenges and innovations in enhancing adherence. Controlled Clinical Trials. (In press).
Manuel JC, Burwell SR, Crawford SL, Lawrence RH, Farmer DF, Hege A, Phillips K, Avis NE. Younger women's perceptions of coping with breast cancer: A mixed methods approach. *Cancer Nursing.* (In press).

Anderson RT, Weisman CS, Camacho F, Scholle SH, Henderson JT, Farmer DF. Distinguishing satisfaction with on-going health care services from visit-specific ratings in women accessing primary care. *Health Services Research.* (In press).

i Bari M, Suggs PK, Holmes LP, Farmer DF, Williams SW, Pahor M, Jackson SA. Research partnership with underserved African-American communities to improve the health of older persons with disability: a pilot qualitative study. Aging Clinical Experimental Research. (In press)

Farmer DF, Reddick B, D'Agostino R, Jr., Jackson SA. Psychosocial correlates of mammography screening in older African American women. Oncology Nursing Forum. (In press)

Farmer DF, Jackson SA, Camacho F, Hall MA. Attitudes of African American and low socioeconomic status white women toward medical research. Journal of Health Care for the Poor and Underserved. (In press)

Fowler TS, Ellis S, Farmer DF, Hege A, Anderson RT, Jones AS. Lessons learned from a faith community-based domestic violence pilot program in Forsyth County, NC. (In press)

Manuscripts Under Review:

Farmer DF, Ip E, Naughton M. Spirituality and quality of life among young women with breast cancer. (Submitted to Psycho-Oncology)

Manuscripts In Preparation:

Danhauer SC, Farmer DF, Crawford S, Avis NE. A longitudinal investigation of coping and quality of life in younger women with breast cancer.

Danhauer SC, Tooze J, Farmer DF, McQuellon RP, Rutherford C, Barrett R, Miller B. Restorative yoga as a supportive intervention for women with ovarian or breast cancer: Findings from a pilot study.

Farmer DF, Burwell S, Vitolins M, Case D. Weight gain among younger women following breast cancer treatment.

Published Abstract:

Farmer D, Petrek JA, Ip E, <u>Naughton MJ</u>. Spirituality in Young Breast Cancer Survivors One to Three Years Post-Diagnosis. Proceedings of the 2005 Era of Hope: Department of Defense Breast Cancer Research Program Meeting, p. 486 (P69-3).

National Research Presentation:

Farmer D, Petrek JA, Ip E, <u>Naughton MJ</u>. Spirituality in Young Breast Cancer Survivors One to Three Years Post-Diagnosis. Era of Hope: Department of Defense Breast Cancer Research Program Meeting. Philadelphia, Pennsylvania. June 11, 2005. (Poster)

Grants:

Factors Affecting Breast Cancer Screening Adherence in Older African American Women. Pilot project funded through the PACRE project and the Comprehensive Cancer Center of Wake Forest University. Co-investigator (no salary support) with Dr. Bobbie Reddick of Winston-Salem State University in Winston-Salem, NC. (August 1, 2004 – July 31, 2005).

Professional Conferences Attended:

- International Society for Quality of Life Research in Prague, Czech Republic, November, 2003
- American Psychosocial Oncology Society in Orlando, Florida, January, 2004
- Cancer Survivorship, Pathways to Health After Treatment, Washington, DC, June, 2004
- Era of Hope: Department of Defense Breast Cancer Research Program Meeting. Philadelphia, Pennsylvania. June, 2005.
- American Psychosocial Oncology Society in Amelia Island, Florida, February, 2006

<u>Master's Courses Audited in the Clinical Epidemiology and Health Services Research Master's Program at Wake Forest University</u>:

Introduction to Epidemiology, Fall, 2003
Advanced Epidemiology and Clinical Trials, Spring, 2004
Introduction to Statistics, Fall, 2003
Applied Linear Models, Spring, 2004
Advanced Statistical Methods, Fall, 2004

Additional Training:

SAS Programming I: Essentials, SAS Institute, Cary, North Carolina, July, 2004
SAS Programming II: Essentials, SAS Institute, Cary, North Carolina, August, 2004
Professional Memberships:

American Psychosocial Oncology Society (APOS)
Society for Behavioral Medicine (SBM)

Quality of Life and Functional Status across the Life Course

Project 1: Menstrual Cycle Maintenance and Quality of Life After Breast Cancer Treatment: A Prospective Study

PRINCIPAL INVESTIGATORS: Michelle J. Naughton, Ph.D.
Kimberly VanZee, M.D.
Elizabeth Naftalis, M.D.
David Euhus, M.D.

About 15% of new breast cancer cases occur in women of childbearing age and the majority will be long-term survivors. For those patients who receive adjuvant chemotherapy, almost half will experience amenorrhea, resulting in infertility, menopausal symptoms, and changes in their life quality. The purposes of this study are: 1) to continue to follow prospectively a cohort of 628 young women, ages 18-45, diagnosed with breast cancer, stages 1-3, recruited through a previous award (DAMD17-96-1-6292); and 2) to recruit an additional 200 women from two participating clinical centers (Memorial Sloan-Kettering Cancer Center in New York, and the University of Texas Southwestern in Dallas, Texas). The major objectives of this study are to track the menstrual bleeding patterns of these young women, identify determinants of treatment-related amenorrhea, track subsequent pregnancies and outcomes, examine the women's quality of life longitudinally, and evaluate the patients' disease-free and overall survival. All participants will be followed for a minimum of 2.5 years to a maximum of 8 years. To our knowledge, this is the largest prospective study of young breast cancer patients being conducted in the United States or elsewhere. At 18 months post-diagnosis, 60% of the patients report some menstrual bleeding. Patients also report arm swelling (30%), hot flushes (56%), and vaginal dryness (43%). Patients' life quality is lower during treatment but improves significantly 12-18 months post-diagnosis.

PART I - INTRODUCTION

About 15% of new breast cancer cases occur in women of childbearing age and the majority will be long-term survivors. For those patients who receive adjuvant chemotherapy, almost half will experience amenorrhea, resulting in infertility, menopausal symptoms, and changes in their life quality. Very little is known about the incidence, onset, time course, and symptomatology of premature menopause induced by breast cancer therapy, or the impact on the young survivor's quality of life. The purposes of this study are: 1) to continue to follow prospectively a cohort of 628 young women, ages 18-45, diagnosed with breast cancer, stages 1-3, recruited through a previous award (DAMD17-96-1-6292); and 2) to recruit an additional 200 women from two participating clinical centers (Memorial Sloan-Kettering Cancer Center in New York, and the University of Texas Southwestern in Dallas, Texas). The major objectives of this study are to track the menstrual bleeding patterns of these young women, identify determinants of treatment-related amenorrhea, track subsequent pregnancies and outcomes, examine the women's quality of life longitudinally, and evaluate the patients' disease-free and overall survival. All participants will be followed for a minimum of 2.5 years to a maximum of 10 years. To our knowledge, this is the largest prospective study of young breast cancer patients being conducted in the United States or elsewhere.

PART II - BODY: STATEMENT OF WORK

Task 1:   Continued Follow-up of Study Participants (Months 1-78):

a. Clinical Center staff will mail follow-up surveys at 6 month intervals, and menstrual bleeding calendars at 3 month intervals to participants already enrolled in the protocol from the previous DOD award (DAMD17-96-1-6292).

The coordinating center personnel at Wake Forest University have continued to mail follow-up forms to previously recruited study participants at the prescribed intervals (i.e., bleeding calendars every 3 months; and study questionnaires every 6 months). The total number of participants who were recruited to this study under the previous award is 628 participants. Patients were recruited from the following clinical centers beginning in January of 1998: Memorial Sloan-Cancer Center in New York City (n=450 participants); M.D. Anderson Cancer Center in Houston, Texas (n=92); Wake Forest University (n=49 participants); and Presbyterian Hospital in Dallas, Texas (n=37 participants). Recruitment ended at Wake Forest University, M.D. Anderson Cancer Center, and Presbyterian Hospital in Dallas on December 31, 1999. The current award permits the additional accrual of 200 patients from only two clinical sites: Memorial Sloan-Kettering Cancer Center in New York City, and a new site, the University of Texas-Southwestern Medical Center and its affiliates.

In general, the participants recruited under the former award are well-educated, with 63% having at least a 4 year college degree. Approximately 55% are employed full-time, and 14% are employed part-time, mostly in professional (51%) or managerial positions (17%). Seventy-five percent of the participants are married or are living in a married-like relationship. Roughly 71% of the participants have children. The average age at recruitment to the study was 39 years

of age. Approximately 88% of the participants are white (non-Hispanic), 5% are African-American, 4% are Hispanic, and 3% are Asian.

The following table provides information on the current follow-up status of the 628 participants accrued previously:

Participation Status	n	%
Active:	390	62.0%
Completing questionnaires and bleeding calendars	266	68.2%
Completing questionnaires only*	124	31.8%
Dropped/Lost-to-Follow-up:	177	28.2%
Deaths	61	9.7%
	628	100.0%

* Participants who have had a hysterectomy or who have not had a menstrual period for 2 continuous years post-treatment complete study questionnaires only

Rates of participant dropout/lost to follow-up have been spread fairly equally across the clinical centers, except for Presbyterian Hospital in Dallas. These patients had to be re-consented in the spring of 2003, and as a result, 9 participants from that site, declined to continue in the study any longer.

	Active	Dropped/Lost to Follow-up	Deaths
Memorial Sloan-Kettering	288 (64.1%)	124 (27.6%)	37 (8.2%)
M.D. Anderson	54 (58.7%)	23 (25.0%)	15 (16.3%)
Wake Forest	30 (60.0%)	16 (32.0%)	4 (8.0%)
Presbyterian Hospital	18 (48.5%)	14 (38.0%)	5 (13.5%)
	390 (62.0%)	177 (28.2%)	61 (9.7%)

Of the 177 persons (28.2%) who have been dropped or lost to follow-up as of May 30, 2006, the following listing provides reasons for study dropouts:

77   could not be reached by mail, phone, or personal contacts (i.e., lost to follow-up)
65   lost interest in participating in the study any longer
7   cited a lack of time
3   cancer recurrence or metastatic disease
2   illness/treatment side effects/other medical problems
4   too overwhelmed to continue participating
2   questions too personal/confidentiality issues
2   personal/family obligations
1   questions were depressing to a participant
1   husband asked her to stop participating
1   poor English
1   upset about her clinical care at her clinical center
1   participant began a 2 year sailing trip and asked to be dropped
9   patients from Presbyterian Hospital who opted not to be reconsented
1   believes study is a waste of time

In January of 2006, we began our 8th year of follow-up on our earlier enrolled participants. We have currently retained approximately 62% of our original participants and have lost 9.7% of our patients to death. Efforts are continuing to try to retain the existing study cohort for additional years of follow-up.

Task 2:   **Study Set-Up/IRB Approvals (Months 1-12):**

a. Review procedures already established for study conduct, patient recruitment, and patient follow-up.

The Manual of Procedures for this study was completed in year 1.

b. Obtain final IRB site-specific approval for this protocol from the University of Texas Southwestern Medical Center and its affiliates in Dallas, Texas.

Site-specific IRB approval for the University of Texas Southwestern Medical Center in Dallas, Texas was approved for the Aston Ambulatory Care Center and the Zale Lipshy University Hospital in July of 2001. Approval to accrue patients from the Parkland Health and Hospital System was obtained on September 17, 2001.

c. Obtain final IRB approval from the DOD for the continued follow-up of previously enrolled participants, as well as for the new recruitment of study participants from Memorial Sloan-Kettering Cancer Center in New York City, and the University of Texas Southwestern Medical Center in Dallas, Texas.

IRB approval from the DOD was obtained for the continued follow-up of patients originally recruited at Wake Forest University, Memorial Sloan-Kettering Cancer Center, and the M.D. Anderson Cancer Center.

Permission to accrue 200 new patients from the Memorial Sloan-Kettering Cancer Center and the University of Texas-Southwestern Medical Center affiliates was approved in September of 2002.

Approval to re-consent 27 active patients, originally recruited from Presbyterian Hospital in Dallas, to the clinical center at Wake Forest University (Dr. Naughton, Principal Investigator), was obtained in April of 2003. This change was made at the request of Dr. James Strauss (PI) of the Presbyterian Hospital Clinical Center.   Participants were sent IRB approved informed re-consent forms and personal health authorization forms. Of these 27 patients, 18 participants agreed to be re-consented, and 9 participants declined to be re-consented for the extended follow-up period. These 9 participants were dropped from our participant tracking system, and no further study materials have been sent to these women.

In August of 2004, Dr. Elizabeth Naftalis, the PI of the University of Texas – Southwestern site left that institution.   On September 1, 2004, Dr. Naftalis was replaced as PI by Dr. David Euhus, Associate Professor in the Division of Surgical Oncology at the University of Texas Southwestern.

Task 3:   **Patient Recruitment   (Months 13-20):**

a.   **Identify eligible patients from patient registries at the Memorial Sloan-Kettering Cancer Center and the University of Texas Southwestern Medical Center.**

Staff at the University of Texas-Southwestern Medical Center was trained on September 9, 2002 in procedures of patient identification, patient recruitment, and patient registration by Dr. Michelle Naughton. Staff persons at this site are continually locating eligible patients from patient rosters.

Staff at Memorial Sloan-Kettering in New York continues to identify eligible participants from their hospital billing records and cancer registries. These staff persons worked on the previous award, and thus did not need to undergo additional training.

b. **Begin the recruitment of eligible patients to the protocol. Patients recruited to the protocol from the clinical centers will be registered online using a web-based system developed by the Biostatistic's Core Facility.**

New patient recruitment ended on December 31, 2005. An additional 209 patients were recruited to the study. Study coordinators at Memorial Sloan-Kettering recruited 188 participants, and staff at the University of Texas-Southwestern Medical Center recruited 21

patients. These patients were registered on-line, using the new registration system developed by the Biostatistic's Core. Thus we have achieved 105% (209/200) of our recruitment goal.

c.   Clinical Center staff will mail baseline, eligibility, and screening forms to the Coordinating Center at Wake Forest University.

Study coordinators at Memorial Sloan-Kettering and UT-Southwestern have mailed the baseline, eligibility, and screening forms to the project managers at the coordinating center at Wake Forest University. Copies of these forms also remain in the patients' files at Sloan-Kettering and UT Southwestern, along with the original copy of the signed informed consent forms. Wake Forest University does not keep copies of the patients' consent forms.

Task 4:   New Patient Follow-up (Months 13-75):

a.   Coordinating Center will mail out bleeding calendars every 3 months, and follow-up questionnaires every 6 months to the newly enrolled participants.

The recruited patients have been entered into the study tracking system, and receive bleeding calendars and questionnaires from staff at the coordinating center at the above specified intervals.

Fifteen of the 209 participants or 7.2% have dropped since enrollment. The reasons for participant dropout are as follows:

5 – no longer interested
4 - cannot be reached
1 - overwhelmed
1 - too much paperwork
1 - didn't want to be reminded of her cancer
3 - deaths

b.   Clinical Center staff will complete the Chart Review Form at 12 months post-recruitment on the newly enrolled patients.

All new participants recruited to the study have Chart Review Forms completed at 12 months post-recruitment. Staff at the participating clinical centers are notified as to when chart review forms are due. Completed forms are mailed to the Project Manager at Wake Forest University for data entry. All remaining chart reviews will be completed by December 31, 2006.

Task 5:   Data Cleaning and Management (Months 1-78):

a.   Biostatistic's Core will perform all data-related tasks, including devising the patient registration, data entry and data management systems. SAS data sets will be developed for interim and final analyses of study data.

The Biostatistic's Core Facility has completed the following tasks for this protocol in the past year:

1) provided a series of error reports to assist in data cleaning and maintaining data quality.
2) prepared interim analyses of study data.
3) maintained SAS data sets of collected study data.
4) completed data analyses of participant menstrual bleeding and amenorrhea, arm and hand swelling, quality of life, and sexual satisfaction and arousal.

Further details about the activities of the Biostatistic's Core can be found in the annual report document from the core facility.

b.   Data cleaning will be performed by the Project Manager's in conjunction with the Biostatistic's Core programmers.

Data cleaning continues on a regular basis in conjunction with the study programmers. Project managers review all baseline and follow-up study forms as they are received from the clinical centers and the study participants, respectively, in order to check for errors or missing data. Participants are contacted if questions about the study forms arise.

Task 6:   Adherence and Retention (Months 1-78):

a.   **Receipt of participants' bleeding calendars and forms will be tracked by staff at the Coordinating Center.**

All enrolled patients are entered into our study tracking system, which cues our study staff when follow-up forms and bleeding calendars are to be mailed to participants. Patient forms are mailed approximately 3 weeks prior to their target completion date in order to allow time for participants to receive the forms in the mail and complete them in their homes. Participants who have not returned their study forms within 14 days of their target completion date, are sent a reminder post-card regarding the study forms.   If the forms have still not been received within 22 days of their target completion date, these participants are called by our Assistant Project Manager to inquire regarding the status of the forms. The Assistant Project Manager works with individual participants who are having difficulty completing study forms, for whatever reason, to try to make the completion of the study requirements as easy as possible.

Study project managers also check all follow-up questionnaires completed by participants to check whether scores on the Beck Depression Inventory are within normal ranges.   During the past 12 months, 9 patients achieved Beck Depression scores above the cutoff score of 15 points. The PIs of the participants' respective institutions were contacted, and the participants were referred to health professionals and/or support groups, if they were not already seeking assistance in controlling depressive symptoms. No adverse outcomes have occurred with any of these 9 patients.

b.   Incentives for maintaining high levels of patient participation in follow-up activities will continue to be devised.

Retention of study participants is paramount in the current protocol. All participants will be followed for a minimum of 3.5 years to a maximum of 10 years. Participants receive no monetary compensation for their participation, but donate their time in completing the study requirements. In addition, the study participants are located in 20+ states in the United States, and two other countries, with no face-to-face contact with study coordinators after their initial study recruitment. Thus, there is no means to reinforce, in-person, the importance of study participation outside of mailed contacts with study staff.

Current Retention Activities Used:

Study Newsletters – are printed and mailed to all study participants on a regular basis. These letters provide updates on study participation, new information regarding issues related to breast cancer, and a "Participant Corner" in which individual participants have volunteered to share their cancer experiences with the other participants. Recently, information has been provided regarding the study results to participants who are 3 years or more beyond their date of recruitment.

Birthday Cards – all participants are sent cards on their birthdays each year.

Special Event Cards - participants are sent cards to celebrate special events in their lives, that they share with us, including weddings, births, receiving a promotion, etc. Similarly, sympathy cards are sent to participants who have experienced a loss, and to the spouses/partners/relative of a study participant who has died.

Quarterly Drawings for Gift Certificates - Quarterly drawings of gift certificates were initiated in January 2000, to provide an additional "boost" to study participation. Study drawings are conducted using the following procedure:

All participants receive some type of mailing (i.e., bleeding diaries or bleeding diaries plus a study questionnaire) from the study coordinating center each quarter. Participants are informed that by returning their diaries and/or questionnaires by the due date listed on the label attached to their forms, that they will be automatically included in a quarterly drawing for gift certificates. Once the participants' packets are mailed back to the coordinating center, the extra ID labels attached to their study forms are cut off by Ms. Carol Corum, the study Project Manager, and are stored in large envelopes designated for the participants' initial recruitment site (i.e., Memorial Sloan-Kettering; Wake Forest; Presbyterian Hospital; M.D. Anderson Cancer Center). At the end of each quarter, seven winners are selected in the following proportions to match the number of participants at each clinical center: 4 winners from Memorial Sloan-Kettering, 1 from Wake Forest, 1 from the patients originally registered through Presbyterian Hospital in Dallas, and 1 from M.D. Anderson Cancer Center. No participants are allowed to receive a prize more than once, and if a repeat winner is drawn, another label is drawn from that site.

After a winner has been drawn, Ms. Corum calls the participants to inform them that they have won the quarterly drawing and to see if they would like to accept a gift certificate. (Only 3 women have declined a gift certificate since the initiation of this incentive.) Participants may choose a gift certificate from: Home Depot, Lowe's Home Improvement, Wal-Mart, or a Long-distance calling card. Because our participant population is geographically diverse, we have chosen large retail chains, so that most participants have 2 or more of these stores in their area from which to choose.

As of March 31, 2006, 170 gift certificates have been provided to study participants.

To date, the participant drawings have gone smoothly, and we have received no complaints from any participants regarding the conduct of these drawings. We are continuing to seek out new ways to provide incentives to the participants in this study, but the drawings have motivated many participants to return their study forms in a timely manner.

c. A study newsletter will continue to be written and sent to all patients at least twice a year.

Study newsletters were sent to all participants in December 2004 and May of 2005. At each of these time points, one newsletter, which contained some preliminary results of the study data, was provided to participants who were 3 or more years beyond study recruitment. A different newsletter, which contained no major study results, was provided to participants who have been recruited less than 3 years. The rationale for including some information about study results is that the newsletters provide another means of giving feedback and information to the participants for their lengthy participation in the trial.

d. **Birthday cards will be mailed to all participants**.

Birthday cards were mailed to all active study participants on their birthdays during this past year.

e. **Holiday cards will be mailed to participants every year.**

A holiday greeting was sent in December 2004 and December 2005.

A Valentine's Day mailing was also completed in February of 2005.

Task 7:   Data Analyses/Manuscript Preparation/ Presentations (Months 6-78):

a.   Abstracts, manuscripts and posters will be prepared from interim data (i.e., data sets comprised of participants 1, 2, 3, and 4 years post-recruitment).

Task is on-going. See below: "PART IV – Reportable Outcomes"

b.   Annual reports will be written to the DOD.

Task completed on May 31, 2006.

Task 8:   Final Analyses and Report Writing, (Months 54-78):

a.   Final analyses of data assessing primary study endpoints will be performed, and manuscripts will be written and submitted for publication in peer-reviewed journals.

Task is underway. See below: "PART IV – Reportable Outcomes"

PART III - KEY RESEARCH ACCOMPLISHMENTS

- 836 women have been recruited to this protocol since 1998, (209 have been recruited under the new award. Retention of the entire study cohort is approximately 62% after up to 101 months of study follow-up. Retention of the newly recruited participants is 92.8% (194/209 participants).

- Menstrual bleeding patterns: Approximately half of all patients were having some menstrual bleeding at approximately 1 year following the end of treatment. Bleeding was highest for those patients who received no chemotherapy, and those who were younger (< 35 years of age) at the time of diagnosis.

- With respect to chemotherapy regimen, menstrual bleeding at 3 years was highest for those receiving adriamycin and cyclophosphamide (AC) or adriamycin, cyclophosphamide and paclitaxell (ACT). Bleeding was lowest for those women who had received cyclophosphamide, methotrexate, and 5-fluorouracil (CMF).

- Menopausal symptoms: At 18-24 months post-diagnosis, approximately half of the participants are reporting some menopausal symptoms. For example, 56% of the patients report hot flushes, 46% report night sweats, 43% report vaginal dryness, 68% report restless sleep, and 63% report mood changes. Reporting of vasomotor symptoms has been increasing during the follow-up period as the participants age and menstrual cycles decrease.

- Pregnancy outcomes: Patients have reported 87 pregnancies during the follow-up period resulting in 54 live births (including 3 sets of twins). There has been 1 infant death, 19 miscarriages, and 4 pregnancy terminations.

- Assisted Reproduction: Three patients have reported 3 surrogate pregnancies and births, (including 1 set of twins). Fourteen participants have elected to adopt children, with 7 more adoptions currently in process.

- Health-related quality of life: Overall, patients' health-related quality of life has been improving as time from diagnosis and treatment increases. Predictors of better quality of life at 1 year post diagnosis are: Caucasian ethnicity, having greater satisfaction with physical appearance, having greater social support, and time since diagnosis. At 2 and 3 years post diagnosis, however, participants who are more highly educated and engage in moderate weekly exercise report better quality of life. Receiving any form of chemotherapy, however, is found to be a negative predictor of quality of life at 2 and 3 years post-diagnosis.

- Sexual Functioning: Approximately 82.7% of participants report being sexually active at approximately 1 year post-surgery for their breast cancer. Participants who were sexually active tended to be married or partnered, to have a smaller tumor size at diagnosis, and to report higher quality of life and social support, and fewer depressive symptoms than those who were sexually inactive.

- Higher sexual arousal at 1 year post-breast cancer surgery was found to be significantly related to having menstrual bleeding, a higher body mass index (BMI), better sleep quality, greater satisfaction with one's physical appearance, and not avoiding physical affection.

- Higher sexual satisfaction at 1 year post-breast cancer surgery was found to be significantly related to having menstrual bleeding, reporting fewer depressive symptoms, greater satisfaction with one's physical appearance, and not avoiding physical affection.

PART IV - REPORTABLE OUTCOMES

1) **Abstracts and poster presentations completed since October 1, 2004:** (See Appendix)

Published Abstracts:

Petrek JA, Case LD, Singletary E, Naftalis D, Paskett D, Naughton MJ. Incidence, Time Course, and Determinants of Menstrual Bleeding after Breast Cancer Treatment: A Prospective Study. Journal of Clinical Oncology, 23(16S – Part I): 13, 2005.

Sukumvanich P, Petrek JA, Naughton MJ, Case D. Incidence and Time Course of Bleeding After Long-Term Amenorrhea Following Breast Cancer Treatment: A Prospective Study. Journal of Clinical Oncology, 23(16S – Part I): 22, 2005.

Naughton MJ, Petrek JA, Ip E, Paskett ED, Naftalis E. Health-Related Quality of Life of Pre-Menopausal Breast Cancer Survivors. Journal of Clinical Oncology, 23(16S – Part I): 37, 2005.

Petrek JA, Naughton MJ, Case LD, Singletary E, Naftalis D, Paskett D. Incidence, Time Course, and Determinants of Menstrual Bleeding after Breast Cancer Treatment: A Prospective

Study. Proceedings of the 2005 Era of Hope Department of Defense Breast Cancer Research Program Meeting, p. 148 (P20-13).

Sukumvanich P, Petrek JA, Naughton MJ, Case D. Incidence and Time Course of Bleeding After Long-Term Amenorrhea Following Breast Cancer Treatment: A Prospective Study. Proceedings of the 2005 Era of Hope Department of Defense Breast Cancer Research Program Meeting, p. 148 (P20-14).

Farmer D, Petrek JA, Ip E, Naughton MJ. Spirituality in Young Breast Cancer Survivors One to Three Years Post-Diagnosis. Proceedings of the 2005 Era of Hope: Department of Defense Breast Cancer Research Program Meeting, p. 486 (P69-3).

MacRae MJ, Case LD, Petrek JA, Naughton MJ. Predictors of Sexual Arousal and Satisfaction among Young Breast Cancer Survivors One Year Post-Surgery. Proceedings of the 2005 Era of Hope: Department of Defense Breast Cancer Research Program Meeting, p. 487 (P69-4).

Naughton MJ, Petrek JA, Ip E, Paskett ED, Naftalis E. Health-Related Quality of Life of Pre-Menopausal Breast Cancer Survivors One to Three Years Post-Diagnosis. Proceedings of the 2005 Era of Hope: Department of Defense Breast Cancer Research Program Meeting, p. 487 (P69-5).

Paskett ED, Abbot J, McCoy T, Petrek JA, Naughton MJ. Arm and Hand Swelling Among Young Breast Cancer Survivors One to Three Years Post-Surgery. Proceedings of the 2005 Era of Hope: Department of Defense Breast Cancer Research Program Meeting, p. 487 (P69-6).

Walsh SR, Ip E, Petrek JA, Naughton MJ. Predictors of Depression in Younger Women with Breast Cancer During the First Two Years Post-Diagnosis. Proceedings of the 2005 Era of Hope: Department of Defense Breast Cancer Research Program Meeting, p. 487 (P69-7).

Research Presentations:

Petrek JA, Case LD, Singletary E, Naftalis D, Paskett D, Naughton MJ. Incidence, Time Course, and Determinants of Menstrual Bleeding after Breast Cancer Treatment: A Prospective Study. 41st Annual Meeting of the American Society of Clinical Oncology. Orlando, Florida. May 16, 2005. (Poster- Discussion Session)

Sukumvanich P, Petrek JA, Naughton MJ, Case D. Incidence and Time Course of Bleeding After Long-Term Amenorrhea Following Breast Cancer Treatment: A Prospective Study. 41st Annual Meeting of the American Society of Clinical Oncology. Orlando, Florida. May 16, 2005. (Poster)

Naughton MJ, Petrek JA, Ip E, Paskett ED, Naftalis E. Health-Related Quality of Life of Pre-Menopausal Breast Cancer Survivors. 41st Annual Meeting of the American Society of Clinical Oncology. Orlando, Florida. May 16, 2005. (Poster)

Naughton MJ, Case LD, Singletary E, Naftalis D, Paskett D, Petrek JA.   Incidence, Time Course, and Determinants of Menstrual Bleeding after Breast Cancer Treatment: A Prospective Study.   Era of Hope: Department of Defense Breast Cancer Research Program Meeting. Philadelphia, Pennsylvania. June 10, 2005. (Presentation and poster)

MacRae MJ, Case LD, Petrek JA, Naughton MJ. Predictors of Sexual Arousal and Satisfaction among Young Breast Cancer Survivors One Year Post-Surgery. Era of Hope: Department of Defense Breast Cancer Research Program Meeting. Philadelphia, Pennsylvania. June 11, 2005. (Presentation and poster)

Paskett ED, Abbot J, McCoy T, Petrek JA, Naughton MJ. Arm and Hand Swelling Among Young Breast Cancer Survivors One to Three Years Post-Surgery. Era of Hope: Department of Defense Breast Cancer Research Program Meeting. Philadelphia, Pennsylvania. June 11, 2005. (Presentation and poster)

Walsh SR, Ip E, Petrek JA, Naughton MJ. Predictors of Depression in Younger Women with Breast Cancer during the First Two Years Post-Diagnosis. Era of Hope: Department of Defense Breast Cancer Research Program Meeting. Philadelphia, Pennsylvania. June 11, 2005. (Presentation and poster)

Naughton MJ, Petrek JA, Ip E, Paskett ED, Naftalis E. Health-Related Quality of Life of Pre-Menopausal Breast Cancer Survivors One to Three Years Post-Diagnosis. Era of Hope: Department of Defense Breast Cancer Research Program Meeting. Philadelphia, Pennsylvania. June 11, 2005. (Poster)

Farmer D, Petrek JA, Ip E, Naughton MJ. Spirituality in Young Breast Cancer Survivors One to Three Years Post-Diagnosis. Era of Hope: Department of Defense Breast Cancer Research Program Meeting. Philadelphia, Pennsylvania. June 11, 2005. (Poster)

Sukumvanich P, Petrek JA, Naughton MJ, Case D. Incidence and Time Course of Bleeding After Long-Term Amenorrhea Following Breast Cancer Treatment: A Prospective Study. Era of Hope: Department of Defense Breast Cancer Research Program Meeting. Philadelphia, Pennsylvania. June 9, 2005. (Poster)

2) Published Journal Articles:

Published Journal Article

Petrek JA, Naughton MJ, Case LD, Paskett ED, Naftalis EZ, Singletary SE, Sukumvanich P. Incidence, Time Course, and Determinants of Menstrual Bleeding After Breast Cancer Treatment: A Prospective Study. Journal of Clinical Oncology. 24:1045-1051, 2006.

Journal Articles Under Review

Farmer D, Ip E, Case LD, <u>Naughton MJ</u>. Spirituality in Young Breast Cancer Survivors One to Three Years Post-Diagnosis. <u>Psycho-Oncology</u>. (Under Review)

Paskett ED, <u>Naughton MJ</u>, McCoy TP, Case LD, Abbott JM. Arm and Hand Swelling Among Young Breast Cancer Survivors One to Three Years Post-Surgery. <u>Cancer Epidemiology, Biomarkers & Prevention</u>. (Under review.)

MacRae MJ, Case LD, Petrek JA, <u>Naughton MJ</u>. Predictors of Sexual Arousal and Satisfaction among Young Breast Cancer Survivors One Year Post-Treatment. <u>Journal of Clinical Oncology</u>. (Under Review)

Sukumvanich P, Case LD, <u>Naughton MJ</u>, Singletary SA, Paskett ED, Naftalis EZ, VanZee K, Petrek JA. Incidence and Determinants of Menstrual Bleeding After 6- and 12-Months of Amenorrhea Following Breast Cancer Treatment. <u>New England Journal of Medicine</u>. (Under Review)

Journal Articles in Preparation:

<u>Naughton MJ</u>, Case D, Ip E, VanZee K, Singletary SA, Paskett ED, Naftalis E. Health-Related Quality of Life of Pre-Menopausal Breast Cancer Survivors Three Years Post-Diagnosis.

Walsh SR, Ip E, <u>Naughton MJ</u>. Predictors of Depression in Younger Women with Breast Cancer during the First Two Years Post-Diagnosis.

PART V - CONCLUSIONS

Further data analyses are planned during 2006-2007 to examine continuing changes in patients' menstrual bleeding patterns, menopausal symptoms, pregnancy attempts and pregnancy outcomes, and health-related quality of life post-treatment.

The results of this research will enable us to answer critical questions regarding the risks (or non-risks) of childbearing after breast cancer, will assist in predicting which women may be more likely to lose their menstrual cycles following breast cancer treatment, and will provide much needed, longitudinal data on the quality of life of young cancer patients following treatment from breast cancer. Few studies have examined the impact of breast cancer diagnosis and treatment on young women long-term. Younger women are at a different life stage than patients in their 60's and 70's, and face different kinds of challenges than older women. Issues such as caring for children in the home, balancing work and family roles, and changes in physical health as a result of cancer or its treatment, (e.g., lymphedema or premature menopause), are concerns of importance to young survivors. The development of interventions to assist women in maintaining optimal quality of life following treatment is critical.

PART VI - REFERENCES

N/A

Quality of Life and Functional Status across the Life Course

Project 2: Investigating mechanisms to explain age associated differences in quality of life among breast cancer patients.

PRINCIPAL INVESTIGATORS: Nancy E. Avis, Ph.D.
                                          Kimberly VanZee, M.D.
                                    David Euhus, M.D.
                                    Michelle Naughton, Ph.D.

ABSTRACT

The primary purpose of this study is to examine mechanisms that may explain age differences in the health-related quality of life of women who have been diagnosed with a first-time breast cancer. The study will examine psychosocial factors such as social support, coping strategies, resiliency, and the impact of cancer on life responsibilities as explanations of age-associated factors affecting HRQL. This project is an observational, longitudinal study of women aged 18 and over who are newly diagnosed with breast cancer. In order to examine both the short- and longer-term impact of breast cancer on HRQL, the study will survey women post diagnosis and follow them at 3, 6, 12, and 18 months. A secondary purpose of the proposed study is to have this large cohort of breast cancer patients serve as a comparison group for the other studies in the Behavioral Center of Excellence. Patients for the proposed study will be recruited from two clinical centers: Memorial Sloan-Kettering Cancer Center (MSK) and University of Texas - Southwestern University (UT-SW).

PART I - INTRODUCTION

The primary purpose of this research is to examine mechanisms that may explain age differences in the health-related quality of life of women who have been diagnosed with a first-time breast cancer. The study examines psychosocial factors such as social support, coping strategies, resiliency, and the impact of cancer on life responsibilities as explanations of age-associated factors affecting HRQL. This project is an observational, longitudinal study of women aged 18 and over who are newly diagnosed with breast cancer. In order to examine both the short- and longer-term impact of breast cancer on HRQL, the study surveys women post diagnosis and follow them at 3, 6, 12, and 18 months. A secondary purpose of the study is to have this large cohort of breast cancer patients serve as a comparison group for the other studies in the Behavioral Center of Excellence. Patients for the study were recruited from two clinical centers: Memorial Sloan-Kettering Cancer Center (MSK) and University of Texas - Southwestern University (UT-SW).

PART II – BODY: STATEMENT OF WORK

The primary activities during this fourth and fifth year of the study have been to complete study recruitment at the Memorial Sloan Kettering Cancer Center and at the University of Texas-Southwestern, and to continue participant follow-up. The tasks described in the original statement of work have not changed. However, time involved in obtaining Human Subjects approval from the Department of Defense was not included as part of the original timeline. This approval has taken an enormous amount of time and has essentially moved the timeline back over a year. Because of these delays, we received additional funding for a 5th project year and a no cost extension. It is important to note that we did not receive Human Subjects approval from the Department of Defense to recruit at University of Texas- Southwestern (UT-SW) until February 2004 and thus had less time for recruitment at that site. We received approval to recruit from Memorial Sloan Kettering in April 2003.

Task 1: Develop research protocol (months 1-15)

a. Finalize research questionnaires

The questionnaires were finalized and submitted with the 2002 report.

b. Review protocol with sites

As stated above, the protocol has been reviewed and approved by the Human Subjects Internal Review Boards (IRB) at all sites. The DOD Office of Human Subjects Protection approved the protocol for Memorial Sloan Kettering Cancer Center in April 2003 and they approved the protocol for the University of Texas – Southwestern in February 2004.

Task 2: Develop data management system (months 3-12)

    a. Develop data management requirements
    b. Develop reporting requirements
    c. Develop contact record
    d. Train data manager

These tasks have all been completed. Please see the Biostatistics Core Report for a review of these ongoing activities.

Task 3: Identify, recruit, and conduct baseline interviews of eligible patients (months 16-33)

    a. Study sites identify and recruit eligible patients
    b. Patients recruited and interviewed

Recruitment has been completed at both sites. Because of the delays in obtaining Human Subjects Approval from DOD we extended recruitment until February 28, 2006, at which time 658 women were recruited to the study. Please see the below table for a distribution by age of study participants. The age category of 18-45 years with no menstrual bleeding was unable to be filled due to much lower than expected rates of hysterectomy and premature menopause in this age group. Recruitment proportions in the other age groups were 72.5%, 98.5%, 84%, and 71.5%, respectively, of our target goals. Even though we did not meet our recruitment goals in each age category, we will have sufficient power to examine quality of life and psychosocial differences by age among our study participants.

Table of Study Recruitment by Age Category as of February 28, 2006

Ages 18-45 (No menstrual bleeding)	Ages 18-45* (Menstrual Bleeding)	Ages 46 – 54 years	Ages 55 – 64 years	Ages 65+ Years	**Total**
4	145	197	168	143	**658**
.1%	22.1%	30.0%	25.6%	21.8%	**100%**

* Participants in the age 18-45 (menstrual bleeding) category are shared with Project 1: Menstrual Cycle Maintenance and Quality of Life Following Breast Cancer Treatment.

    c. Quality control (ongoing)

Quality control is an ongoing activity. See the Biostatistics Core Report for a review of these ongoing activities.

    d. Medical record review

Medical record review is completed at both sites 12 months from the date of the participants' recruitment. This task is ongoing, and will be completed for all participants in March of 2007.

e. Data entry system developed

This task has been completed for both sites.

f. Data entry of questionnaires (ongoing)

This task is being completed for the recruited participants.

Task 4: Ongoing follow-up of patients (months 19-73)

a. Tracking of women in study
b. Mailing of follow-up questionnaires

All women who have been recruited have been entered into a tracking data base. Follow-up forms are mailed at 2 ½ , 5 ½ 11, and 17 months following baseline – for the 3- and 6-, 12 and 18- month follow-ups.   To date, only 13 women have dropped out of the study. Reasons for study drop-out were:

Not interested (6)
Illness/treatment side effects (1)
Could not be reached (2)
Death (4)

The following table shows the number of follow-up questionnaires completed to date:

	3 mo. FU		6 mo. FU		12 mo. FU		18 mo. FU	
	N	%	N	%	N	%	N	%
Due	0	0.0%	4	0.6%	0	0.0%	8	1.2%
Due and out of window	35	5.3%	39	5.9%	43	6.5%	50	7.6%
Due and booklet returned	623	94.7%	568	86.3%	441	67.1%	368	55.9%
Not due	0	0.0%	46	7.0%	174	26.4%	232	35.3%
Not due-booklet returned	0	0.0%	1	0.2%	0	0.0%	0	0.0%
Total	658		658		658		658	

c. Contacting non-responders

Women who do not return their survey by the due date are sent a postcard reminder. Follow-up phone calls are made if forms are not received 10 days after the postcard reminder is sent.

d. Mailing of incentives

A drawing for gift certificates is held each quarter to reward participants for returning follow-up questionnaires. All participants who return their questionnaire booklets in a given quarter are entered into a drawing for a $50 gift certificate from one of the following vendors: Lowe's

Home Improvement, Home Depot, Wal-Mart, and a Long Distance Phone card.   To date, we have mailed out 45 gift certificate incentives. Only two people have refused a gift certificate.

   e. Follow-up medical record reviews

   Medical record review is completed at both sites 12 months from the date of the participants' recruitment. This task is ongoing, and will be completed for all participants no later than June 1, 2007.

Task 5: Data Analysis and Report Writing (months 33-73)

   a. Data entry of questionnaires received from the participants:

       Task on-going through October 31, 2007

   b. Data management and merging of baseline, follow-up and medical chart review forms:

       Data files will be merged to create baseline and follow-up data files for statistical analyses at periodic intervals between May 1, 2006 and October 31, 2007.

   c. Data cleaning:

       The project managers will work with the programmer in the Biostatistic's Core to conduct data cleaning during the creation of the study data sets.

   d. Data analysis:

       Baseline data cleaning and analysis will begin in the summer of 2006. Follow-up data analysis is expected to begin during late 2006 and early 2007. Data analysis will continue after the end of the DOD grant funds.

   e. Presentation of results at professional meetings:

       Task to be initiated in 2007.

   f. Initial manuscripts prepared:

       Manuscripts will be prepared in the next 12 months using baseline quality of life data. Some examination of the short-term follow-up endpoints (e.g., 6 week, 3 and 6 months) regarding the quality of life and psychosocial outcomes, may also be initiated within the next 12 month period.

PART III - KEY RESARCH ACCOMPLISHMENTS

- Completion of study recruitment
- Good retention of study participants from the 3 – 18 months follow-up assessment time points.

PART IV - REPORTABLE OUTCOMES

None

Part V - CONCLUSIONS

This section is not applicable at this point.

PART VI - REFERENCES

Not applicable

Quality of Life and Functional Status across the Life Course

Project 3: Research on Optimal Recovery Practices in Breast Cancer (RESTORE)

PRINCIPAL INVESTIGATORS: Roger T. Anderson, Ph.D.
                           Paul Ribisl, Ph.D.

ABSTRACT

Breast cancer is one of the most prevalent diseases among women, and one of the most feared. Although society has benefited from advances in medical and surgical treatments leading to increased survivorship, there has been a general lag in the development of post treatment health care programs to improve the quality of life for women following breast cancer. RESTORE focuses on two issues post-surgery that affect the lives of women with breast cancer: quality of life and lymphedema. There is now ample data in the literature on fatigue, emotional distress, and the recovery phase from the diagnosis of cancer and its treatment to conclude that for at least some women psychosocial issues may be significant and lasting posing additional barriers to recovery from cancer. Further, as the majority of women now receive axillary node dissection, risk for lymphedema (swelling of the arm), leading to pain, psychological distress, and impairment of physical, vocational, social and sexual functioning is increasingly important. The goal of this project is to test whether a combined intervention program can improve health-related quality of life and physical functioning for women newly diagnosed with breast cancer. This program is a tailored exercise program, which includes a lymphedema prevention program, and patient education. Results from this study will be used to recommend post-operative cancer care strategies to enhance well-being and quality-of-life for women.

Part I – INTRODUCTION

Breast cancer is one of the most prevalent diseases among women. Although advances in medical and surgical treatments have led to increased survivorship, there has been a general lag in the development of post-operative health care programs. This research project tests an intervention (with a control group) designed to enhance the quality of life and physical well-being of adult women recently treated for breast cancer in the Piedmont Triad region of North Carolina. We randomized 100 women with stages I to III breast cancer one of the following: (1) usual care consisting of patient education, and 2) a comprehensive program of tailored exercise. Identification of eligible women occurred through medical and surgical oncologists' offices and are Piedmont Triad cancer treatment centers. Age and stage eligible women will be enrolled 6 to 12 weeks post surgery and followed for 18 months. The exercise programs are center-based and tapered to home sessions to promote high adherence levels by integration into daily life. The Comprehensive Tailored Exercise Program focuses on improving muscle strength and flexibility, and the swelling prevention program focuses specifically on arm exercises, massage techniques, and wearing of an elastic sleeve. Outcomes include change from baseline in the 6-minute walk test, and the FACT-B (Functional Assessment of Cancer Therapy – Breast) health-related quality of life scale during the 18-month period following randomization.

Part II – Body: ORIGINAL STATEMENT OF WORK

Task 1. Identify, contact, and recruit eligible women

a. Recruit and consent eligible patients into the study (a 28-month period inclusive of months 09-36).

Status: Task Completed. 105 participants have been recruited to this study. Originally, 200 participants were to be recruited to this trial. However, changes in surgical practice patterns from the more standard use of axillary node dissection to the use of sentinel node dissection, necessitated that the lymphedema primary outcome be removed from the study. This reduced the sample size needed to assess the quality of life and fitness outcomes to 100 participants. This sample size reduction was approved by the Wake Forest University Institutional Review Board, and by the DOD Human Subjects review board in March and April of 2004, respectively. The revision was formally enacted after the additional approval by the RESTORE Data Safety Monitoring Board (DSMB) in May 2004. Project data will still be sufficient to statistically determine if the exercise intervention is associated with changes in arm swelling.

Task 2. Conduct Baseline 1 visit.

a. Schedule participant visits to Reynolda Campus for baseline visit 1 to assess fitness and Health-Related Quality of Life (HRQL).

Status: COMPLETED

Task 3. Conduct 3-month visit: Baseline 2.

a.   Assess QOL, fitness, swelling, anthropometrics and health status:

    Status: COMPLETED.

b.   Assess resting metabolism and diet at GCRC:

    Status: 20 participants are completing this activity June 1 - October 30, 2006.

c.   Conduct baseline DEXA scan:

    Status: COMPLETED

Task 4. Conduct Tailored Exercise Program (CTEP) to CTEP group.

a.   Develop and begin tailored physical activity.

    Status: COMPLETED.

Task 5. Conduct 6-month follow-up visit.

a.   Assess QOL, fitness, swelling, anthropometrics and health status.

    Status: COMPLETED

Task 6. Conduct 9-month follow-up visit. End center-based exercise phase.

a.   Assess QOL, fitness, swelling, anthropometrics and health status.

    Status: COMPLETED

b.   Begin home-based exercise phase.

    Status: 20 participants will complete this activity June 1 through August 31, 2006.

Task 7. Conduct 12-month Telephone Call.

a.   Assess Fatigue and HRQL.

    Status: 20 participants will complete this activity June 1 - August 31, 2006.

Task 8. Conduct 15-month follow-up visit. (months 18-44).

a.   Assess QOL, fitness, swelling, and health status.

   Status: 20 participants will complete this activity June 1 - October 31, 2006.

Task 9. Conduct final visit. (Months 21-47).

a.   Assess QOL, fitness, swelling, and health status.

    Status: 20 participants will complete this activity June 1 - October 31, 2006.

b.   Assess resting metabolism and diet at GCRC.

   Status: 20 participants will complete this activity June 1 - October 31, 2006.

c.   Conduct DEXA scan.

   Status: 20 participants will complete this activity June 1 - October 31, 2006

Task 10. Create analytic database.

a.   Develop study forms for web-based data entry.

   Status: Ongoing. Task will be completed by November 30, 2006.

Part III. KEY RESEARCH ACCOMPLISHMENTS

- 105 patients have been recruited to the study.

- The final 20 participants will complete the study by October 31, 2006.

Part IV. REPORTABLE OUTCOMES

Adverse Events

We have reported 12 adverse events, of which 3 were SAEs. None of these events were determined to be likely related to RESTORE. IRB filings have been made for each case.

Paper Presentations:

Strayer SL et al. Exercise and Older Women with Breast Cancer: Influences on Self-Esteem. Paper presented at the Annual Meeting of the Southeastern Region of the American College of Sports Medicine, Charlotte, North Carolina, January, 2005.

Anderson RT. Retention and Adherence in Clinical Trials. Paper presented at the American Association of Cancer Researchers (AACR), Baltimore, Maryland, November, 2005.

Part V. CONCLUSIONS

N/A

Part VI. REFERENCES

N/A

Quality of Life and Functional Status across the Life Course

Biostatistics Core Facility

PRINCIPAL INVESTIGATORS: L. Douglas Case, Ph.D.

ABSTRACT:

The overall objective of the Biostatistic's Core Facility for this Behavioral Center of Excellence is to collaborate with investigators in each project throughout all phases of the research. Major responsibilities are assumed for statistical, methodological, logistical, and computer related issues including study design, data collection, quality control, database development and management, data analysis, and manuscript preparation, each of which is vitally important to the success of the BCE. The Core Facility has been and will continue to be involved in all phases of these projects. Staff members have collaborated with individual investigators in defining objectives for each research project, defining end points to quantify treatment effect, selecting appropriate information for data collection, determining sample sizes that ensure adequate power, and developing randomization schemes that ensure valid treatment comparisons. The Core Facility will continue to be involved in these studies during their execution and analysis.

PART I - INTRODUCTION

The main objective of the Biostatistics Core Facility is to collaborate with the investigators of each project in the analysis, interpretation, and reporting of study data collected during the grant period. Staff members initially collaborated with individual investigators in defining objectives for each research project, defining end points to quantify treatment effect, selecting appropriate information for data collection, refining data collection forms, determining sample sizes that ensured adequate power, and developing randomization schemes that ensure valid treatment comparisons. Subsequently, staff members collaborated with the investigators in designing and programming a web-based data entry and tracking system, implementing quality control features, and performing preliminary analyses. During this continuation phase, we will continue to collect follow-up data and enter it into the system and perform quality control checks. However, the major focus will be to analyze data from all studies and write papers for publication. The Biostatistics Core will be primarily responsible for analyzing the data and for writing the statistical methods and results sections for each paper

PART II – BODY: STATEMENT OF WORK

Task 1:   Study Design (Month 1)

a. **Help formulate primary and secondary study hypotheses and define important outcome variables;**
b. **Determine sample sizes that ensure adequate power;**
c. **Develop randomization schemes that ensure valid treatment comparisons.**

Completed in Year 1

Task 2:   Protocol and Form Development (Months 2 – 3)

a. **Assist with the development of Manual of Operations. Manuals of Procedure will be developed which will clearly define all procedures and contingency plans. All procedures will be tested before accrual of any patients.**
b. **Help develop concise, easily understood data collection forms. Assess their inter- and intra-tester reliability.**

Completed in Year 1

Task 3:   Database Setup (Months 4 - 10)

a. **Design and implement a computer database management system. A computer database will be established that allows web-based data entry.**
b. **Design and implement quality control procedures for data checking, storing and updating data while maintaining security and confidentiality.**

- Completed the design in Year 1; this database continues to be maintained and enhanced with additional functionalities**.**
- Maintain security measures on data collected in all three projects. All data entered into the web site is saved onto a secure database server located in the Department of Public Health Sciences. The server is located behind the Wake Forest University Health Sciences' firewall and the data is backed up to tape nightly. These tapes are stored onsite in a fireproof cabinet for 2 weeks, after which they are moved offsite. Offsite, the tapes are stored in a lock box, in a vault, maintained by WFUSM Information Services.   The web site utilizes Secure Socket Layer Encryption software to encrypt data moving to and from each user's PC. Website security authorization complies with HIPAA regulations. Access to each area of the web site is determined by access privileges based on role and is stored in a SQL Server database.

Task 4:   Data Management (Months 11 – 40)

    a. **Perform interim analyses and provide feedback to the investigators regarding patient accrual and quality control.**
    b. **Tabulate and summarize measures of protocol adherence and numbers of dropouts for coded treatment group assignment and, when available, record reasons for lack of adherence or dropping out.**
    c. **Develop graphical reports that dynamically show actual vs expected accrual. Develop programs to monitor for unexpected side effects and adverse events.**
    d. **Check and clean data as they are collected.**

Interim analyses of data from the Menstrual Cycle Maintenance Study (Project 1) continued during the last year, leading to presentations, abstract, drafts of papers, manuscript submissions, and publications. (See the Appendix for copies of these documents.)

Tracking reports listing participant adherence and the receipt of participants' forms continue to be run weekly, so that participants can be contacted by coordinating center personnel if forms have not been received by their deadline dates.

Dropped participants reports are run for each project.

Quality Control Checks:

Menstrual Cycle Maintenance (Project 1):

We continue to perform quality control checks on the Menstrual Cycle Maintenance data. SAS programs were previously developed to check the validity of data within each form and to provide extensive error checking for chart reviews, demographic, medical history, medical history follow-up, symptoms, quality of life, and diary forms.

Age Differences (Project 2):

Quality control features were built into the screens (e.g., range checks, field checks, skip patterns, etc.) to allow data validation at the point of data entry. Also, validation error reports were implemented, displaying outstanding errors for all forms, by Participant ID.

Restore (Project 3):

Quality control features were programmed (e.g., range checks, field checks, skip patterns, etc.) to allow data validation at the point of data entry. Batch processing of errors will be implemented to check for errors in all the data that has been entered to date.

Task 5:   **Analysis and Report (Months 41 – 73)**

     a. **Convert the database to SAS and ASCII data sets for final analyses.**
     b. **Help develop a publications and presentations policy.**
     c. **Perform final data analyses and help prepare manuscripts and reports.**

Once all the data have been collected, edited, and corrected, a final SAS database will be created, including documentation for variable names and transformations. SAS transport and ASCII datasets will also be created to ensure maximum portability. These datasets will be stored on tape and on CDs (or the medium appropriate at that time). These tasks will be completed during the carryover period as follow-up is completed.

New Task 6: Continuation of Analysis and Reporting (Months 49 – 73)

Data analysis and manuscript preparation will take the majority of our efforts in the remaining grant months. Planned papers include: the baseline paper for the Restore study (Project 3); the effect of the exercise intervention on quality of life and physical function (Project 3); the effect of the exercise intervention on arm swelling (Project 3); the effect of chemotherapy on menstrual bleeding patterns (Project 1); fertility following cancer treatment (Project 1); the baseline paper from the age differences study (Project 2); and the effect of age on quality of life and coping following breast cancer diagnosis and treatment (Project 2).

PART III – KEY RESEARCH ACCOMPLISHMENTS

- Analyses were completed on published abstracts and paper and poster presentations in 2005-2006 for the Menstrual Cycle Maintenance Study. (See Appendix for copies of these materials.)
- Continued analysis and manuscript writing of the clinical and quality of life outcome data for the Menstrual Cycle Maintenance Study (Project 1).

- Began analysis of the baseline paper for RESTORE (Project 3).

PART IV – REPORTABLE OUTCOMES

Abstracts and papers using analyses performed by the Biostatistics Core are reported in the summaries of each project and are provided in the Appendix.

PART V - CONCLUSIONS

During the last year, more focus was placed on data analysis, and papers have been written on bleeding over time, amenorrhea, swelling, sexual function, and quality of life. Patient follow-up is continuing for all projects. During the next 18 months, follow-up will be completed and analyses will be done to address the primary and secondary aims of each study.

PART VI – REFERENCES

N/A

APPENDIX

Published Abstracts and Poster Presentations

SPIRITUALITY IN YOUNG BREAST CANCER SURVIVORS ONE TO THREE YEARS POST-DIAGNOSIS

Deborah Farmer, Jeanne Petrek, Edward Ip, Michelle Naughton
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Background. Religion and spirituality are increasingly studied as factors in quality of life. Spirituality encompasses a general sense of peace and connectedness and exists both within and outside religious frameworks. Spirituality affects how patients adjust to diagnoses and treatment and is associated with less stress, better physical outcomes, greater longevity, hope and positive mood states. Developing a spiritual framework is an important aspect of the illness experience for many cancer patients and survivors. The purpose of this investigation was to investigate what demographic, clinical and lifestyle factors predict spirituality among younger breast cancer patients, the stability of spirituality over time, and predictors of changes in spirituality.

Methods. The Menstrual Cycle Maintenance and Quality of Life Study enrolled 627 women ages 18-45 years with stage 1-3 breast cancer between 1998 and 2001 and continues to follow them. The current study uses data from the first three years post diagnosis. Demographic (age, race, education, marital status), clinical (lumpectomy, mastectomy, stage, chemotherapy, radiotherapy, reconstructive surgery), lifestyle (social support, smoking, alcohol consumption) and quality of life (SF-12 Health Status Questionnaire) variables were used to predict spirituality using multivariable regression analyses. Spirituality was measured using an abbreviated version (7 items) of the Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being Scale (FACIT-Sp).

Results. Approximately 91% of the patients indicated a religious preference at entrance to the study. The mean score on the abbreviated FACIT-Sp at one year post-diagnosis was19.91 (SD 6.4) (out of 28 total points possible), suggesting a moderately high degree of spirituality among the participants. Predictors of higher spirituality were older age (p=.0085), African-American status (p=.0061), higher social support (p<.0001), consuming less alcohol per month (p=.0035), and better mental (p<.0001) and physical health (p<.0001) as measured by subscales of the SF-12. Having had a mastectomy was a predictor of lower spirituality at one year post-diagnosis (p=.0053). In examining changes in spirituality over the first three years post-diagnosis, spirituality was found to have a small but significant increase (19.9, SD 6.4 year 1 to 20.5, SD 6.2 at year 3, p=.023). Increases in spirituality were seen among women who consumed less alcohol per month and who reported better mental health during the first three years following diagnosis.

Discussion. The findings of this study are consistent with previous literature in spirituality and religiosity that indicate that spirituality is higher in older age groups, those with a better health status, and among African-Americans. The finding that mastectomy was related to a decreased

level of spirituality is unique to breast cancer. The moderately high levels of spirituality at one year post diagnosis and the stability of spirituality over the first three years post-diagnosis suggest that interventions, supportive services, and/or educational materials that incorporate elements of spirituality during treatment and follow-up, may be important factors in patient management.

ARM AND HAND SWELLING AMONG YOUNG BREAST CANCER SURVIVORS ONE TO THREE YEARS POST-SURGERY

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Background: As advances are made in the treatment of cancer, the number of patients who will become survivors will increase. This is especially the case among women with breast cancer where it is estimated that there are nearly two million breast cancer survivors in the United States. An area that has been understudied among breast cancer survivors is lymphedema, a condition that causes swelling and pain in the arm or hand on the side of the breast cancer. Good estimates of lymphedema incidence, prevalence, duration and causative factors are lacking.

Methods: 627 premenopausal women were recruited to the Menstrual Cycle Maintenance and Quality of Life Study between 1998 and 2001 and are still receiving follow-up. Patients were 18-45 years old with regular menstrual cycles at the time of diagnosis with a stage 1-3 breast cancer. Extensive demographic, clinical, and psychosocial data are being collected on these women at 6-12 month intervals, including self-report questions regarding arm and hand swelling. Descriptive analyses were completed to estimate the prevalence of arm and hand swelling at 6 month intervals following surgery, and longitudinal multivariate logistic regression was completed to investigate factors associated with swelling (yes/no) through three years post-surgery.

Results. Approximately half of the patients reported ever having arm and/or hand swelling during the first 36 months post-surgery. Prevalence of arm and/or hand swelling in any six month period following surgery was approximately 25%. Factors associated with ever swelling during the first 36 months post-surgery were being married (OR=2.77, p=.01), and having a higher number of lymph nodes removed (OR=1.05, p=.01). Having an income less than $50,000 (OR 1.61, p=.05) and having a lumpectomy (OR=2.43 p=.05) were borderline significant factors. Women who reported arm or hand swelling also had significantly lower health-related quality of life, as measured by the FACT-B, during the first three years following surgery (p<.01).

Conclusions. These data indicate that patient reports of arm and hand swelling occur among a large proportion of young breast cancer survivors during the first three years post-surgery. Interventions aimed at the prevention and early diagnosis of swelling are needed to improve the health-related quality of life of cancer survivors.

PREDICTORS OF DEPRESSION IN YOUNGER WOMEN WITH BREAST CANCER DURING THE FIRST TWO YEARS POST-DIAGNOSIS

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Background: Depression is one of the most prevalent psychiatric disorders among women with breast cancer and is more pronounced among women aged 50 years and younger. Few longitudinal studies have identified predictors of depression at multiple time points among younger breast cancer survivors.

Methods: 542 women with stage I-III breast cancer who were diagnosed at <46 years of age completed the Beck Depression Inventory (BDI) at 1 and 2 years following diagnosis. Predictors of depression were examined in multivariate analyses as measured by the BDI summed score. Independent variables included demographics (age, education, race, marital status, number of children), clinical variables (stage at diagnosis, type of surgeries and adjuvant treatments, BMI, menstrual bleeding status, time since diagnosis), and psychosocial factors (satisfaction with appearance, social support, sleep quality, quality of life (SF-12), smoking per day, alcohol use per month, exercise).

Results: 13.1% of women at 1 year post-diagnosis and 12.3% at 2 years post-diagnosis reported having depression as measured by a score of 16 or higher on the BDI. Mean BDI scores improved from 1 year post-diagnosis (8.6, SD 6.4) to 2 years post-diagnosis (7.7, SD 6.7, p=.0003). Predictors of depression that were consistent during both the first and second year post-diagnosis were a lower BMI (p=.0279 year 1, p=.0066 year 2), poorer sleep quality (p<.0001 years 1 and 2), dissatisfaction with appearance (p<.0001 years 1 and 2), inadequate social support (p<.0001 years 1 and 2), and worse physical (p=.0192 year 1, p<.0001 year 2) and mental (p=.0002 year 1, p=.0008 year 2) health, as measured by the mental health and physical health subscales of the SF-12. A factor that only predicted depression at 1 year post-diagnosis was not having reconstructive surgery (p=.0291). In addition, having had a mastectomy (p=.0489) was only a significant predictor of depression at year 2.

Conclusions: While the prevalence of depression was low in this sample, women who did report depression had BDI scores indicating moderate to severe depression. Most predictors of depression were consistent at 1 and 2 years post-diagnosis. Findings suggest that interventions targeting dissatisfaction with appearance, increasing social support, improving sleep quality and mental and physical health my benefit younger women with breast cancer who experience depression following diagnosis.

HEALTH-RELATED QUALITY OF LIFE OF PRE-MENOPAUSAL BREAST CANCER SURVIVORS ONE TO THREE YEARS POST-DIAGNOSIS

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Background: Longitudinal studies of the health-related quality of life (HRQL) of premenopausal breast cancer patients are sparse, and are needed to identify survivorship issues among younger women. Younger women are at different life stages than the majority of breast cancer patients, which may result in different challenges post-treatment.

Methods: 627 premenopausal women were recruited to the Menstrual Cycle Maintenance and Quality of Life Study between 1998 and 2001 and are still receiving follow-up. Patients were 18 - 45 years old with regular menstrual cycles at the time of diagnosis with a stage 1-3 breast cancer. Demographic (age, race, education, marital status, number of children), clinical (stage at diagnosis, type of surgery, treatments received, menstrual bleeding status at follow-up), and lifestyle variables (body mass index, cigarette use, alcohol use, exercise and social support) were used in multivariate regression analyses to predict HRQL, as measured by the FACT-B total score, at 1 - 3 years post-breast cancer diagnosis.

Results: FACT-B total scores improved as the time from diagnosis increased (105.5, SD 19.2 at baseline vs. 113.4, SD 19 at year 3, $p<.001$). At one year post-diagnosis, Caucasian race ($p=.0477$), patients' satisfaction with appearance ($p<.0001$), and greater social support ($p<.0001$) were significant predictors of better HRQL. Longitudinal analyses examining cumulative data from baseline to 2 years and baseline to 3 years post-diagnosis, indicated that HRQL was lower among those who received adjuvant chemotherapy ($p=.0150$ year 2; $p=.0174$ year 3). HRQL was higher among Caucasians ($p=.0006$ year 2; $p=.0016$ year 3), those who were more satisfied with their appearance ($p<.0001$ at both years 2 and 3), those who engaged in moderate weekly exercise ($p=.0081$ year 2; $p=.0006$ year 3), those who had higher social support ($p<.0001$ at both 2 and 3 years), and as time from diagnosis increased ($p=.0007$ year 2; $p<.0001$ year 3).

Conclusions: The HRQL of breast cancer survivors is improving as time from diagnosis increases. Survivors with lower levels of social support, and those who received adjuvant chemotherapy may need continuing interventions to improve their HRQL. Interventions focused on increasing satisfaction with appearance, promoting regular physical exercise, and improving social supports may be of benefit to young breast cancer survivors.

INCIDENCE AND TIME COURSE OF BLEEDING AFTER LONG TERM AMENORRHEA FOLLOWING BREAST CANCER TREATMENT: A PROSPECTIVE STUDY

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A gynecological work-up for pathological causes of vaginal bleeding is commenced if a woman has had no menstrual period for 12 months. In lieu of clinical studies, this recommendation stands even for young women with amenorrhea due to chemotherapy.

Five hundred and ninety-five US women ages 20-45 were accrued from January 1998 to July 2002 within 8 months of diagnosis with Stages I-III breast cancer (median follow-up 45 months). Daily bleeding and spotting records were obtained throughout the study. Baseline extensive clinical, demographic, and treatment data (with each drug, dose, and date) were obtained and there was followup every six months. Episodes of vaginal spotting were excluded from analysis. Kaplan-Meier analysis was used to estimate the incidence of at least one bleeding episode after various intervals of prolonged amenorrhea.

The median age of patients was 39.5 years old (range 20-45 years old). Twenty-nine percent of the patients became amenorrheic for 12 months after chemotherapy with no significant difference seen among the three regimens (31%, 20% and 29%) in the AC (doxorubicin, cyclophosphamide), ACT (doxorubicin, cyclophosphamide, taxol) and CMF (cyclophosphamide, methotrexate, 5-FU) respectively. Forty-two percent of the AC group bled within the following four years as compared to 33% and 16% in the ACT and CMF treated patients respectively. Twenty-two percent of the patients experienced an initial two-year period of amenorrhea; only 9% of these women bled in the ensuing three years. Younger women were more likely to bleed after prolonged amenorrhea when analyzed with a repeated measures logistic regression ($p=.03$) and Cox proportional hazards model ($p=.03$).

A considerable portion of patients treated with chemotherapy have at least one bleeding episode despite an initial 12 months of amenorrhea as demonstrated in this study with daily bleeding records. Given this high proportion, a negative gynecological work-up for uterine pathology may not be unexpected especially in younger women and those treated with AC and ACT more than those treated with CMF. This prospective study is the first to provide information that bleeding is common after chemo-induced amenorrhea (29% overall). More research is necessary to make recommendations pertaining to the appropriate work-up of vaginal bleeding after chemotherapy-induced amenorrhea.

PREDICTORS OF SEXUAL AROUSAL AND SATISFACTION AMONG YOUNG BREAST CANCER SURVIVORS ONE YEAR POST-SURGERY

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Background: Sexual functioning among premenopausal survivors of breast cancer has been understudied. Adjuvant chemotherapy may result in premature menopause in many younger patients, with accompanying changes in sexual functioning, such as vaginal dryness or decreased sexual desire.

Methods: 627 premenopausal women were recruited to the Menstrual Cycle Maintenance and Quality of Life Study between 1998 and 2002. Participant follow-up is still ongoing. Patients were 18-45 years old with regular menstrual cycles at the time of diagnosis with a stage 1-3 breast cancer. Multiple regression analysis was used to determine the impact of demographic, clinical, surgical, treatment and psychosocial variables on patients' sexual arousal and satisfaction, as measured by subscales of the Watts Sexual Functioning Questionnaire, at 1 year post-surgery.

Results: For these analyses, data were available on 485 women who had been followed 1 year post-surgery. Of these 485 patients, 401 (83%) reported being sexually active. Sexually active women were significantly more likely to the married/partnered (p<.0001), to have smaller tumors at diagnosis (p=.03), and to report higher quality of life as measured by the FACT-B (p<.0001) and higher social support (p<.0001) than sexually inactive participants. Among the sexually active women, better sexual arousal was predicted by maintaining some menstrual bleeding following treatment (p<.0001), a higher body mass index (BMI) (p=.001), better sleep quality (p=.003), greater satisfaction with appearance (p=.01), and not avoiding physical affection (p=.01). Sexual satisfaction was found to be higher among those receiving mastectomy with radiation therapy compared to those receiving lumpectomy (p = .01) or mastectomy without radiation therapy (p = .03), patients who maintained some menstrual bleeding (p=.01), those reporting fewer depressive symptoms (p<.0001), patients more satisfied with their appearance (p=.02), patients who did not avoid sexual contact (p=.02), and patients whose partners did not avoid sexual contact (p=.002).

Conclusions: Both physical and psychosocial factors are significant predictors of sexual arousal and satisfaction among young women treated for breast cancer. Results from this study may better educate and inform premenopausal patients, as well as practitioners, about changes that may be experienced following treatment. Interventions aimed at improving women's feelings about their sexual attractiveness, and increasing communication between partners post-treatment would be of value.

INCIDENCE, TIME COURSE, AND DETERMINANTS OF MENSTRUAL BLEEDING AFTER BREAST CANCER TREATMENT.   A PROSPECTIVE STUDY

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There has been no trial yet designed to evaluate ovarian function as a primary endpoint and to compare systemic adjuvant therapies concurrently. 595 U S women ages 20 - 45 years were accrued from January 1998 to July 2002 within 8 months of diagnosis with Stages I – III breast cancer (median follow up 40 months) and daily bleeding records were obtained. Baseline extensive clinical, demographic, quality of life and treatment data (with each drug, dose and date of adjuvant chemotherapy) was obtained with follow up every six months. Repeated measures logistic regression was used to assess which variables were predictive of monthly bleeding and to generate probability plots of expected monthly bleeding over time.

Significantly different proportions of women had monthly bleeding depending upon their age (p<.001), chemotherapy program and time interval after that program, as shown in the accompanying graph. In the month after the standard course of doxorubicin and cyclophosphamide (AC) whether or not followed by paclitaxel (T) or docetaxel (R), approximately 16% had monthly bleeding compared to the immediate month after a standard course of cyclophosphamide, methotrexate, 5-fluorouracil (CMF), in which 48% bled (p<.001). Following the three AC programs, there was a slow recovery phase of about 9 months followed by a plateau during which almost half continued monthly bleeding for the remainder of the study follow-up compared to after CMF in which there was no recovery phase and a continual decline in bleeding to about 18% of women with monthly bleeding at study end (p<.001) compared to the AC programs. After chemotherapy there was a small effect of monthly bleeding with tamoxifen use which varied with time. Probability graphs of monthly bleeding in hypothetical patients 30, 35, 40 and 45 years of age treated with each of the four treatment regimens were generated.
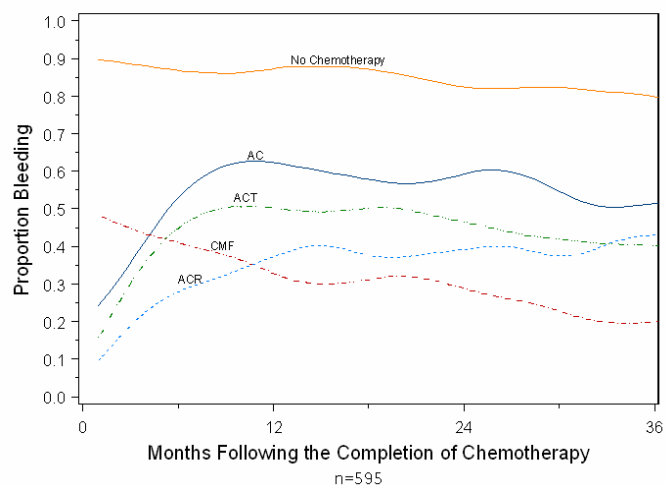
Using daily bleeding records, it is demonstrated that age and the specific adjuvant program impact ovarian function. This unique data set enabled us to produce probability plots from which clinicians can predict the chances of menstrual cycle maintenance in an individual patient.

Incident, Time Course, and Determinants of Menstrual Bleeding After Breast Cancer Treatments: A Prospective Study

Jeanne A. Petrek, M.D.,[1] L. Douglas Case, Ph.D. ,[2] Electra D. Paskett, Ph.D.,[3]
Elizabeth Naftalis, M.D.[4] , and Michelle J. Naughton, Ph.D., [2]

[1] Memorial Sloan-Kettering Cancer Center, [2] Wake Forest University School of Medicine; [3] Ohio State University; [4] University of Texas Southwestern

Purpose and Sample

Purpose:
1) To compare prospectively the effects of current systemic adjuvant therapies on menstrual bleeding after breast cancer treatment.
2) To determine predictors of bleeding following breast cancer treatment.

Sample:
Data are taken from the Menstrual Cycle Maintenance and Quality of Life Following Breast Cancer Treatment Study, which was initiated in 1998. This is an ongoing, multicenter prospective study of premenopausal breast cancer patients, who were recruited from the following clinical centers:
1) Memorial Sloan-Kettering Cancer Center;
2) Wake Forest University; 3) M.D.Anderson Cancer Center; 4) Presbyterian Hospital in Dallas, Texas; and 5) the University of Texas Southwestern.

Measures

A. Monthly Menstrual Bleeding Calendar:
Patients complete monthly bleeding calendars recording the frequency, duration, and amount of menstrual flow each month.

B. Medical Chart Review:
Extensive chart reviews were completed at 1 year post-diagnosis to record breast pathology, histology, surgeries, treatment regimens and dosages, co-morbidities, cancer recurrences, metastases or new diagnoses of cancer.

C. Patient Questionnaires:
Patients complete quality of life, medical and reproductive update forms at 6 month intervals until the end of study.

Inclusion Criteria

• Females
• Ages 18 - 45 years at the time of a first diagnosis of breast cancer.
• Diagnosis of invasive disease Stages I, II, III within the previous six months.
• Having regular menstrual cycles at the time of breast cancer diagnosis. (Women who have had a hysterectomy are excluded from participation.)

Data Analyses

• Data analyses were completed on 595 participants who were recruited between January, 1998 and July , 2002.
• Median follow-up time was 45 months.
• Repeated measures logistic regression was used to assess which variables predicted monthly bleeding over time and to generate probability plots.

Results

Description of Participants:
• Average age at recruitment was 39.5 years (range: 20-45 years).
• 88% non-Hispanic White; 5% African-American; 4% Hispanic; and 3% Asian/Pacific Islander
• 66% have a 4 year college degree or higher.
• 63% have had 1 or more full-term births
• Tumor size: 65% (≤ 2 cm); 30% (2-5 cm); 5% (>5 cm)
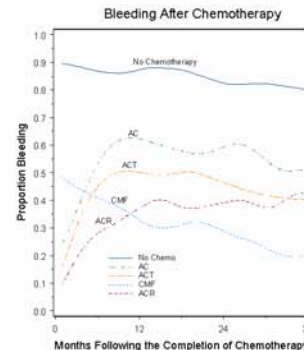• Breast Surgery: 51% lumpectomy; 21% mastectomy with radiation therapy; 28% mastectomy without radiation therapy

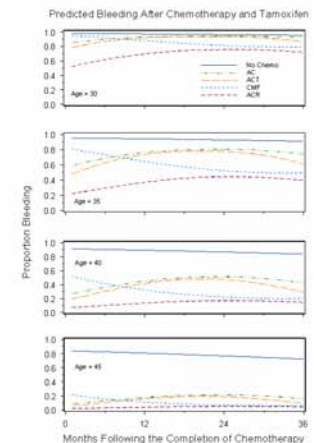## Chemotherapy Regimens

Most Common Chemotherapy Regimens:

AC	=	adriamyacin + cyclophosphamide
ACT	=	adriamyacin + cyclophosphamide + taxol
ACR	=	adriamyacin + cyclophosphamide + taxotere
FAC	=	fluouracil + adriamyacin + cyclophosphamide
FACT	=	5-fluouracil + adriamyacin + cyclophosphamide + taxol
CMF	=	cyclophosphamide + methotrexate + 5 fluouracil

Table 1. Mean Proportion of Months with Menstrual Bleeding Following the End of Chemotherapy

Chemotherapy Regimen	1st Year After Tx Mean (SD)	2nd Year Mean (SD)	3rd Year Mean (SD)
AC	.53 (.38)	.59 (.40)	.59 (.40)
ACT	.30 (.37)	.50 (.42)	.43 (.43)
CMF	.44 (.30)	.30 (35)	.25 (.36)
Age at Diagnosis			
< 35 years	.72 (.31)	.86 (.25)	.87 (.28)
35-40 years	.50 (.36)	.55 (.39)	.54 (.40)
> 40 years	.21 (.29)	.28 (.36)	.22 (.33)

Bleeding After Chemotherapy

Menstrual Bleeding

Predicted Bleeding After Chemotherapy and Tamoxifen

Conclusions

•Significantly different proportions of women had monthly bleeding depending upon their age, chemotherapy program and time interval from the completion of therapy. (See Table 1.)

•After the completion of the three AC regimens (i.e.., AC, ACT, ACR), there was a slow recovery phase of about 9 months followed by a plateau during which about half continued monthly bleeding. For CMF, there was no recovery phase, but only a continual decline in bleeding over time. (See figure at left.)

•Tamoxifen use decreased menstrual bleeding, and its effects varied over time and by age.

Spirituality in Young Breast Cancer Survivors One to Three Years Post Diagnosis

Deborah F. Farmer[1], Ph.D., Jeanne Petrek[2], M.D., Edward Ip[1], Ph.D., Michelle Naughton[1], Ph.D.

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WAKE FOREST
UNIVERSITY
SCHOOL *of* MEDICINE
THE BOWMAN GRAY CAMPUS

Background

Religion and spirituality are increasingly studied as factors in quality of life. Spirituality encompasses a general sense of peace and connected-ness and exists both within and outside a religious framework. Spirituality affects how patients adjust to diagnoses and treatment and is associated with less stress, better physical outcomes, greater longevity, hope and positive mood states. Developing a spiritual framework is an important aspect of the illness experience for many cancer patients and survivors. The purpose of this study was to investigate:

➤ demographic, clinical, psychosocial and lifestyle factors that predict spirituality among younger breast cancer patients;

➤ the stability of spirituality over time; and

➤ predictors of changes in spirituality

Methods

The Menstrual Cycle Maintenance and Quality of Life Study enrolled 627 women ages 18-45 years (mean age = 38.5) with stage 1-3 breast cancer between 1998 and 2002 from four clinical centers. Additional patient recruitment and follow-up continues.

The participants were mostly Caucasian (88%), married or living in a marriage like relationship (75%), and well-educated (65.7% had a college or post-graduate degree). About half (54.8%) were employed full-time.

The current study uses data from the first three years post-diagnosis. Demographic (age, race, education, marital status), clinical (surgery and treatment type, cancer stage), psychosocial (social support, depression, sleep quality, appearance, mental and physical health) and lifestyle (smoking, alcohol consumption) variables were used to predict spirituality using multivariable regression analyses.

Spirituality was measured using an abbreviated version (7 items) of the Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being Scale (FACIT-Sp).[5]

Results

Approximately 91% of the patients indicated a religious preference at entrance to the study.

➤The mean score on the abbreviated FACIT-Sp at baseline was 19.61 out of 28 possible points, suggesting a moderately high degree of spirituality.

➤ Spirituality was found to have a small but statistically significant increase over time (i.e., 19.61, SD 5.93 at baseline to 20.57, SD 5.99 at year 3).

Spirituality (with Meaning and Faith Subscales)
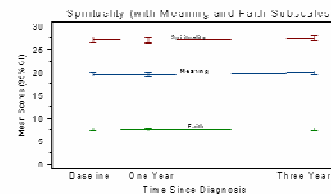
Predictors of higher spirituality during the first three years post-diagnosis were:

➤ being African American (p=.0039) or Hispanic (p=.0002)
➤ having a mastectomy with reconstruction vs lumpectomy (p=.0004)
➤ having a religious affiliation (<.0001)
➤ having more social support (p<.0001)
➤ being less depressed (p<.0001)
➤ being more satisfied with one's appearance (p<.0001)
➤ having better physical (.0199) and mental health (<.0001) health
➤ consuming less alcohol (p=.0470) and
➤ smoking fewer cigarettes (.0502)

Discussion

The findings of this study are consistent with previous literature on spirituality and health that indicate that:
spirituality is higher among those with better mental and physical health status,
among African-American and Hispanic than among Whites, and among those who are affiliated with an organized religion, and that it is inversely associated with current levels of drinking and smoking. Women who had fewer depressive symptoms, more social support, who has a mastectomy with reconstructive surgery rather than a lumpectomy, and who were more pleased with their appearance had higher levels of spirituality.

The moderately high levels of spirituality at baseline and the stability of spirituality over the first three years post-diagnosis suggest that interventions, supportive services, and/or educational materials that incorporate elements of spirituality during treatment and follow-up may be important factors in patient management.

Predictors of Sexual Arousal and Satisfaction Among Young Breast Cancer Survivors One Year Post-Surgery

Marla J. MacRae, M.S.[1], L. Douglas Case, Ph.D.[1], Jeanne A. Petrek, M.D.,[2] and Michelle J. Naughton, Ph.D., [1]
[1] Wake Forest University School of Medicine [2] Memorial Sloan-Kettering Cancer Center

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Purpose and Sample

Purpose: To examine the impact of demographic, clinical, and psychosocial measures on the sexual arousal and sexual satisfaction of pre-menopausal breast cancer patients one year post-surgery.

Sample:
Data were taken from the Menstrual Cycle Maintenance and Quality of Life After Breast Cancer Treatment Study. This is a multi-center, prospective observational study of pre-menopausal women diagnosed with breast cancer. Eligibility criteria were: Females, between the ages of 18-45 years, with a diagnosis of stage I, II, or III breast cancer within the previous 6 months. All participants had regular menstrual cycles at the time of diagnosis. Patient recruitment was initiated in 1998 and will continue through 2005.

Measures

• Monthly bleeding calendars from the time of study
   entry
• Medical history, lifestyle and quality of life updates at 6 to 12 month intervals until study end.
• Dependent Variables:
   Sexual Arousal and Sexual Satisfaction were measured from the Watts Sexual Functioning Questionnaire.

Arousability was measured by 4 items symptoms concerning vaginal dryness and painful intercourse.

Satisfaction was measured by 3 items assessing how often the patient feels satisfied after sexual activity, her contentment with the frequency of sexual activity, and by her frequency of feeling tense or nervous after a sexual experience.

Higher scores indicate better sexual functioning.

Data Analyses

• Analyses were based on 485 participants recruited between January, 1998 and June, 2002, who had complete data through approximately 1 year post-surgery (i.e., 9-15 months post-surgery).

• Chi-square tests for categorical variables and t-tests for continuous variables were assess differences among sexually active vs. sexually inactive participants. Data were analyzed using multiple linear regression to assess the impact of demographic, clinical, and psychosocial variables on sexual arousal and sexual satisfaction.

Results: Sample

• Average age of the women at recruitment was 41 years (range: 21-45)
• 65% have achieved a 4 year college degree or higher
• 89% are white, 4% are African-American, 4% are Hispanic, and 3% are Asian/Pacific Islander
• 76% were married or partnered
• Type of surgery: 52% lumpectomy, 20.5% mastectomy with radiation, 27.5% mastectomy without radiation
• 70% had immediate reconstructive surgery

Sexually Active vs. Sexually Inactive Patients:

• Of the 485 participants, 401 indicated they had been sexually active with a partner in the past 6 months

• As compared to the sexually inactive patients, the sexually active women were:
   • younger (p=.05)
   • had a higher body mass index (BMI) (p=.05)
   • married (p<.0001).
   • had a larger tumor size (p=.05)
   • had reported menstrual bleeding within the previous 90 days (p=.05),
   • had a better overall quality of life (p<.0001)
   • fewer depressive symptoms (p=.02)
   • had greater social support (p<.0001).

Results: Sexual Arousal and Satisfaction

Predictors of Better Sexual Arousal

• Having some menstrual bleeding within the previous 90 days (p<.0001),
• Higher BMI (p=.001),
• Better sleep quality (p=.003),
• Greater satisfaction with appearance (p=.01), and
• Women who did not avoid physical affection (p=.01)

Predictors of Greater Sexual Satisfaction

• Participants who underwent mastectomy with radiation therapy versus a lumpectomy (p=.03)
• Having some menstrual bleeding within the previous 90 days (p=.01)
• Fewer depressive symptoms (p<.0001)
• Better satisfaction with appearance (p=.02)
• Women who did not avoid physical affection (p=.02)
• Women whose partners did not avoid physical affection (p=.002)

Full and Reduced Regression Models for Sexual Arousal

Variable	Full Model β	Full Model p value	Reduced Model β	Reduced Model p value
Demographic				
Age	-0.0575	.20		
Race (W vs B)	-0.7246	.16		
Education (≥ College vs < College)	-0.0045	.99		
Clinical				
Primary Treatment		.11		
Mastectomy w/o RT vs Lumpectomy	-0.5861			
Mastectomy with RT vs Lumpectomy	0.9744			
Nodes Positive		.58		
1-3 vs 0	0.0928			
4+ vs 0	-0.6680			
Tumor Size		.08		
(2-5) vs ≤ 2	-0.9854			
> 5 vs ≤2	-0.4002			
Chemotherapy	-0.6623	.33		
Hormone Therapy	-0.2266	.60		
Time Since Surgery (Months)	-0.1354	.27		
Menstrual Bleeding	1.4708	.003	1.8811	<.0001
BMI	0.1546	.001	0.1412	.001
Change in Weight (lbs)	-0.0005	.98		
Psychosocial				
Depression	-0.0688	.10		
Sleep Quality	-0.0792	.06	-0.1151	.003
Social Support	-0.0101	.42		
Appearance	0.0583	.10	0.0762	.01
Physical Affection				
I avoid it	-0.2163	.06	-0.2340	.01
My partner avoids it	-0.1010	.43		

Full and Reduced Regression Models for Sexual Satisfaction

Variable	Full Model β	Full Model p-value	Reduced Model β	Reduced Model p-value
Demographic				
Age	0.0067	.80		
Race (W vs B)	-0.1529	.68		
Education (≥ College vs < College)	-0.2966	.23		
Clinical				
Primary Treatment		.15		.02
Mastectomy w/o RT vs Lumpectomy	0.2119		0.0700	
Mastectomy with RT vs Lumpectomy	0.7887		0.7289	
Nodes Positive		.52		
1-3 vs 0	-0.2326			
4+ vs 0	0.1707			
Tumor Size		.12		
(2-5) vs ≤ 2	-0.5309			
> 5 vs ≤ 2	0.1341			
Chemotherapy	-0.1555	.69		
Hormone Therapy	-0.0040	.99		
Time Since Surgery (Months)	-0.0136	.85		
Menstrual Bleeding	0.5148	.07	0.5582	.01
Change in Weight (lbs)	-0.0081	.41		
Psychosocial				
Depression	-0.0492	.0002	-0.0979	<.0001
Sleep Quality	-0.0314	.16		
Social Support	-0.0004	.94		
Appearance	0.0287	.16	0.0404	.02
Physical Affection				
I avoid it	-0.1428	.03	-0.1423	.02
My partner avoids it	-0.2451	.001	-0.2232	.002

Conclusions

• Maintaining menstrual bleeding was predictive of both sexual arousal and sexual satisfaction.
• A higher body mass index was a significant predictor of sexual arousal, whereas dissatisfaction with appearance was negatively associated with both sexual arousal and satisfaction.
• Interventions focusing on improving patients' satisfaction with their appearance, treating menopausal symptoms (if present), and improving patient-partner communication regarding sexuality may improve patients' sexual functioning post-surgery.

Predictors of Depressive Symptoms in Younger Women with Breast Cancer During the First Two Years Post-Diagnosis

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Department of Public Health Sciences

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PURPOSE

To determine demographic, medical, and psychosocial predictors of depressive symptoms in younger women with breast cancer (age ≤ 45) at 1 year and throughout 2 years post-diagnosis.

METHODS

· Sample
  · 628 women participated in a prospective longitudinal cohort study
  · Women completed a mailed survey at 3 time points:
    · Within 5-6 months post-diagnosis (baseline)
    · 1 and 2 years following baseline
· Eligibility Criteria:
  · Age 18-45 at diagnosis
  · Diagnosed with a first breast cancer, stage I-III, within previous 6 months
  · Receiving treatment for breast cancer
· Measures
· Sociodemographics
  · Age, partner status, number of children, employment status, occupation, income, level of education
· Psychosocial Measures
  · Beck Depression Inventory (BDI)
  · Sleep Disturbance Scale
  · Satisfaction with Appearance
  · Social Support Scale
  · SF-12 Physical and Mental Health Subscales
  · Personal Habits Questionnaire
· Medical Factors:
  · Stage at diagnosis, type of surgery, reconstruction, type of treatment, time since diagnosis, menopausal status, Body Mass Index (BMI)
· Analyses
  · Descriptive statistics assessed BDI scores over time
  · T-tests tested significance of BDI change scores
  · Linear regression assessed factors associated with depressive symptoms
  · Repeated measures modeled predictors over time

RESULTS

Sample Characteristics

Characteristic	# (%)	Characteristic	# (%)
Clinic		**Income**	
Sloan-Kettering	426 (72)	< 50K/Year	168 (29)
MD Anderson	86 (14)	50-100K/Year	222 (38)
Wake Forest	47 (8)	> 100K/Year	194 (33)
Presbyterian	36 (6)		
Median Age in Years	39.5 (20 – 45)	**Employment**	
Age at Diagnosis in Years		Unemployed/Looking	16 (3)
20 – 24	2 (<1)	Full-time Homemaker	101 (17)
25 – 29	36 (6)	Full-time	325 (55)
30 – 34	108 (18)	Part-time	85 (14)
35 – 39	174 (29)	Disabled	37 (6)
≥40	275 (46)	Other	30 (5)
Median BMI in kg/m²	23.2 (16.9 – 56.9)	**Breast Surgery**	
		Lumpectomy	306 (51)
Marital Status		Mastectomy with Radiation therapy	122 (21)
Single/Separated/Widowed	146 (25)	Mastectomy without Radiation therapy	167 (28)
Married/Marriage-like	449 (75)		
Race/Ethnicity		**Cancer Stage**	
Caucasian	526 (88)	I	372 (65)
African-American	28 (5)	II	169 (30)
Hispanic	25 (4)	III	28 (5)
Asian/Pacific Islander	16 (3)		

Mean Summed BDI Scores Over Time

	N	Mean (SD)	Range	P-value
Baseline	626	10.0 (6.8)	0-42	
Year 1	542	8.6 (6.4)	1-38	.0005
Year 2	512	7.7 (6.7)	0-43	<.0001

Predictors of Depressive Symptoms at 1 Year Post-Diagnosis

	Beta	p-value
Stage	0.41	.4395
Mastectomy	1.03	.2437
Lumpectomy	-0.10	.8970
Reconstruction	-1.72	.0291
Chemotherapy	0.05	.9526
Radiation	-0.33	.6702
BMI (baseline)	-0.13	.0279
Days since dx	-0.00	.3136
Sleep Quality	0.33	<.0001
Smoking per day	0.63	.0845
Alcohol per month	0.00	.8373
Exercise (moderate)	-0.03	.8868
Appearance	-0.32	<.0001
Social support	-0.10	<.0001
Physical SF-12	-0.13	.0192

Predictors of Depressive Symptoms from Study Entry to Year 2 Post-Diagnosis

	Beta	p-value
Stage	0.63	.3064
Mastectomy	2.18	.0489
Lumpectomy	0.77	.3803
Reconstruction	-0.24	.7894
Chemotherapy	-1.76	.0742
Radiation	1.38	.1491
BMI (baseline)	-0.18	.0066
Days since dx	-0.01	.0847
Sleep Quality	0.29	<.0001
Smoking per day	0.52	.2025
Alcohol per month	-0.00	.9636
Exercise (moderate)	-0.20	.3542
Appearance	-0.33	<.0001
Social support	-0.10	<.0001
Physical SF-12	-0.33	<.0001

SUMMARY

· Overall, the percentage of women who reported depressive symptoms was low (12-13%).
· However, women who did report symptoms had moderate to severe symptoms of depression.
· Most of the predictors at year 1 and through year 2 were the same with the following exceptions:
  · Not having reconstructive surgery predicted more depressive symptoms at year 1
  · Having had a mastectomy and worse physical health were predictive of depressive symptoms from study entry to year 2.
· Interventions targeting social support and body image are needed to help younger women following breast cancer diagnosis.

Conclusions

· The severity of depressive symptoms should be assessed and treated in this population.
· Psychosocial interventions are needed to build and maintain social support for younger women and to improve body image following treatment.
· There is a need for collaboration between oncologists and mental health providers to meet the biopsychosocial needs of younger women with breast cancer.

Incidence and Time Course of Bleeding After Long-Term Amenorrhea Following Breast Cancer Treatment: A Prospective Study

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ABSTRACT

Introduction: We examined the incidence of subsequent bleeding in premenopausal patients who became amenorrheic after breast cancer treatment with the current standard chemotherapy regimens.

Methods: Five hundred and ninety-five women age 20 to 45 years were enrolled from January 1998 to July 2002 within 8 months of breast cancer stages I to III diagnosis (median follow-up, 40 months) and daily bleeding records were obtained. Extensive clinical, demographic, quality of life and treatment data (with each drug, dose, and date) were obtained at baseline and follow-up every 6 months. Kaplan-Meier analysis was used to estimate the incidence of bleeding after prolonged amenorrhea.

Results: The median age of the patients was 39.5 years (range, 20-45 years) with a median BMI of 23.2 kg/m2 (range, 16.9-56.9 kg/m2). The majority of patients were treated with AC (doxorubicin, cyclophosphamide), ACT (doxorubicin, cyclophosphamide, paclitaxel), or CMF (cyclophosphamide, methotrexate, 5-FU). Twenty-nine percent of the patients became amenorrheic for at least 1 year after the completion of the chemotherapy treatment. Twenty-two percent of the patients experienced an initial two-year period of amenorrhea; only 9% of these women bled in the ensuing 3 years. No significant difference was seen between the 3 regimens with regard to the onset of amenorrhea (31%, 20% and 29% in the AC, ACT and CMF groups respectively). Forty-two percent of patients in the AC group bled within the following 4 years as compared to 33% in the ACT group and 16% in the CMF group (P<.001).

Conclusion: This is the first prospective study to date documenting the incidence and natural history of bleeding after chemotherapy-induced amenorrhea. A considerable portion of patients treated with chemotherapy can resume bleeding despite an initial 12 months or even 24 months of amenorrhea. This is more common after treatment with AC and ACT compared to CMF. Given the high portion of patients with bleeding, a negative gynecologic work-up in these patients may not be unexpected. It may not always be necessary to intensively workup women who bleed for the possibility of uterine pathology.

BACKGROUND

- Cytotoxic chemotherapy can improve overall survival in breast cancer patients; the greatest improvement occurs in premenopausal women.
- Ovarian failure may result from such treatment leading to chemotherapy-related amenorrhea (CRA).
- Information on CRA is an important part of the counseling of premenopausal women receiving chemotherapy. Patients with CRA can have improvement in overall survival as well as associated side effects such as vasomotor symptoms, sexual dysfunction, and premature bone loss.
- The current literature on CRA is based on retrospective data from many trials with varying chemotherapy regimen and doses.
- Prospective data is lacking on the rates of amenorrhea in patients treated with modern chemotherapeutic regimens, including combination therapy with taxanes.

OBJECTIVE

To prospectively examine the effects of current commonly used chemotherapy regimens on menstrual cycles in premenopausal women being treated for breast cancer.

METHODS

- This prospective study assesses menstrual bleeding in premenopausal breast cancer patients age 18-45 years with regular menstrual cycles treated with adjuvant chemotherapy from 1998 to 2002.
- Patients complete daily bleeding records from the time of study recruitment until study end.
- Clinical information including patient demographics, stage and treatment-related information such as radiation therapy and chemotherapy were also obtained.
- Statistical Methods: Records from 6 months and 1 year following the end of chemotherapy were examined to determine if any bleeding (light, medium, or heavy) occurred during that time. Those women without any bleeding for that time were considered to have treatment-related amenorrhea. Ensuing records were then examined to determine the women's subsequent bleeding status over time. Kaplan-Meier methods were used to estimate the time to subsequent bleeding following the initial (6 month, 1 year, etc.) amenorrheic episode. Log-rank tests were used to assess differences between patients treated with different chemotherapy regimens in the time to bleeding resumption. Cox's proportional hazards regression model was used to determine which characteristics were jointly predictive of subsequent bleeding. Only patients with complete bleeding records for the entire 6 months and 1 year of amenorrhea were included in this analysis.

RESULTS

627 women were initially accrued, 32 patients failed to return any daily bleeding records and were excluded from the analysis. Of the 595 remaining patients, 523 patients received cytotoxic chemotherapy as part of their treatment for breast cancer. Of the 523 patients who received cytotoxic chemotherapy, 24 patients dropped out of the study and 124 patients did not have complete diary data for at least 6 months following the completion of chemotherapy. This left a total study population of 375 patients available for analysis.

Figure 1. Amenorrhea following chemotherapy

Forty percent of patients receiving chemotherapy had no menstrual bleeding in the 6 months following the end of chemotherapy. A majority of patients who were not initially amenorrheic continued to have menstrual bleeding.
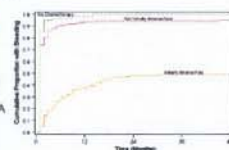
Table 1. Patient demographics.

| Characteristic	n	Initial 6-month amenorrhea (%)	P-value	n	Initial 12-month amenorrhea (%)	P-value
Total	375	151 (40)		310	91 (29)	
Clinic						
Sloan-Kettering	273	107 (39)		226	63 (28)	
MD Anderson	57	20 (35)		48	12 (25)	
Wake Forest	26	14 (54)		24	10 (42)	
Presbyterian	19	10 (53)	.265	12	6 (50)	.179
Age at Diagnosis in Years						
(20 – 35)	86	9 (10)		62	1 (2)	
(35 – 40)	116	34 (29)		97	18 (19)	
≥40	173	108 (62)	<.001	151	72 (48)	<.001
BMI.*						
Underweight/Normal (<25)	256	92 (36)		214	55 (26)	
Overweight (25-29.9)	75	43 (57)		60	29 (48)	
Obese (30+)	44	16 (36)	.003	36	7 (19)	.001
Race/Ethnicity						
Caucasian	325	127 (39)		267	76 (28)	
African-American	15	6 (40)		11	3 (27)	
Hispanic	22	10 (45)		20	6 (30)	
Asian/Pacific Islander	13	8 (62)	.410	12	6 (50)	.458
Smoke 100 Cigarettes						
No	207	78 (38)		165	40 (24)	
Yes, Former Smoker	142	57 (40)		122	41 (34)	
Yes, Current Smoker	26	16 (62)	.065	23	10 (43)	.069
Age at First Menstrual Period						
≤11	79	30 (38)		69	22 (32)	
12	115	45 (39)		97	24 (25)	
13	119	50 (42)		102	28 (27)	
≥14	62	26 (42)	.928	42	17 (40)	.273
Full Term Births						
0	138	53 (38)		111	28 (25)	
1+	237	98 (41)	.575	199	63 (32)	.233
Nodes Pos						
0	187	62 (33)		158	33 (21)	
1-3	122	52 (43)		100	35 (35)	
4-9	39	18 (46)		30	12 (40)	
10+	27	19 (70)	.002	22	11 (50)	.004
Chemotherapy Regimen						
AC	70	28 (40)		58	13 (22)	
ACT	123	54 (44)		103	30 (29)	
ACR	15	7 (47)		9	4 (44)	
FAC	28	10 (36)		26	6 (23)	
FACT	24	7 (29)		20	5 (25)	
CMF	67	24 (36)		56	18 (32)	
Other	48	21 (44)	.784	38	15 (39)	.531
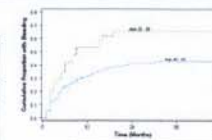
Figure 2. Subsequent Menstrual bleeding in patients with an initial 6-month period of amenorrhea following chemotherapy stratified by age

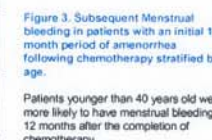Patients older than 40 years old are less likely to resume menstrual bleeding than patients younger than 40 years old.

Figure 3. Subsequent Menstrual bleeding in patients with an initial 12-month period of amenorrhea following chemotherapy stratified by age.

Patients younger than 40 years old were more likely to have menstrual bleeding 12 months after the completion of chemotherapy.
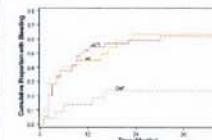
Figure 4. Subsequent Menstrual bleeding in patients with an initial 6-month period of amenorrhea following chemotherapy stratified by chemotherapy regimen.

Fewer patients on CMF regimen had resumption of menstrual bleeding following an initial 6-month period of amenorrhea as compared to AC or ACT.
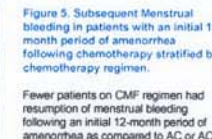
Figure 5. Subsequent Menstrual bleeding in patients with an initial 12-month period of amenorrhea following chemotherapy stratified by chemotherapy regimen.

Fewer patients on CMF regimen had resumption of menstrual bleeding following an initial 12-month period of amenorrhea as compared to AC or ACT.

CONCLUSIONS

This is the first prospective study to date documenting the incidence and natural history of chemotherapy induced amenorrhea. A considerable proportion of patients treated with chemotherapy can resume bleeding despite an initial 6 or 12 month amenorrheic episode. Newer treatment regimens such as AC-T appear to have a higher resumption of bleeding as compared to CMF. Given this high proportion of bleeding, a negative gynecologic work-up in these patients may not be unexpected.

JOURNAL OF CLINICAL ONCOLOGY

Incidence, Time Course, and Determinants of Menstrual Bleeding After Breast Cancer Treatment: A Prospective Study

Jeanne A. Petrek†, Michelle J. Naughton, L. Douglas Case, Electra D. Paskett, Elizabeth Z. Naftalis, S. Eva Singletary, and Paniti Sukumvanich

A B S T R A C T

Purpose
To assess ovarian function using the surrogate of monthly bleeding after breast cancer treatment in premenopausal women.

Patients and Methods
Five hundred ninety-five US women age 20 to 45 years were accrued from January 1998 to July 2002 within 8 months of diagnosis with stages I to III breast cancer (median follow-up 45 months). Daily bleeding records were obtained prospectively, as well as extensive clinical, demographic, quality of life, and treatment data. Repeated measures logistic regression was used to assess which variables were predictive of monthly bleeding.

Results
Significantly different proportions of women had monthly bleeding depending on their age ($P < .001$), chemotherapy program ($P < .001$), and time since treatment regimen. In the month after the standard course of doxorubicin and cyclophosphamide (AC), whether or not followed by paclitaxel or docetaxel, approximately 16% had monthly bleeding compared with the cyclophosphamide, methotrexate, fluorouracil (CMF) group, in which 48% bled ($P < .001$). Following any AC regimen, there was a slow recovery phase of about 9 months followed by a plateau, during which almost half continued monthly bleeding for the remainder of the follow-up period compared with after CMF in which there was no recovery phase and a continual decline in monthly bleeding to approximately 18% of women at study end ($P < .001$). Tamoxifen use decreased bleeding between months 12 and 24 after chemotherapy with 15% fewer women having bleeding.

Conclusion
Using daily menstrual bleeding records, it is demonstrated that age, the specific chemotherapy regimen received, and tamoxifen use impact ovarian function.

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INTRODUCTION

With advances in treatment, most breast cancer patients will be long-term survivors.[1] For premenopausal patients, their quality of life can be disrupted by premature, chemotherapy-induced ovarian dysfunction, resulting in vasomotor symptoms, disrupted sleep, dyspareunia, dysuria, and vaginitis. Younger breast cancer survivors are known to experience more psychosocial distress than older women,[2-4] and the menopausal transition and infertility may be important components of this distress.[5-6]

The incidence, time course, and determinants of ovarian dysfunction are not as well studied as the life-threatening complications of systemic therapy, such as cardiotoxicity or leukemogenesis. Even when it is reported, amenorrhea is noted as one of many secondary end points gathered in trials designed to assess other outcomes.[7] Weaknesses of past research include small numbers of young women in chemotherapy trials, varying definitions of end points (eg, oligomenorrhea, amenorrhea), varying intervals of data collection, and limited lengths of follow-up. Recent reviews on chemotherapy-related amenorrhea found rates from 21% to 100%,[7-8] suggesting little precision in these estimates. The possible quality-of-life advantage with maintenance of ovarian function must be considered along with conflicting research that shows a survival benefit of chemotherapy-related amenorrhea in some studies,[9-10] and not in others,[11-13] as well as the benefit of ovarian suppression as an alternative to chemotherapy

1045

in premenopausal women with hormone-receptor positive early-stage breast cancer.[14,15]

We report results from one of the first prospective studies using daily records of menstrual bleeding in premenopausal women to assess which therapies and clinical and demographic factors affected the maintenance of menstrual bleeding up to 5 years post-treatment.

PATIENTS AND METHODS

Participants were recruited to a multicenter, longitudinal observational study assessing menstrual cycle maintenance and quality of life after breast cancer treatment. Inclusion criteria were female patients, age 18 to 45 years, who were diagnosed with stages I to III invasive breast cancer within the previous 8 months. Exclusions were any prior or concurrent history of any cancer, excluding basal or squamous cell skin carcinoma and stage 0 cervical cancer. Participants were required to have regular menstrual cycles at the time of diagnosis. Thus, women who had a previous hysterectomy, even with intact ovaries, were ineligible for this protocol.

Recruitment to this study began in January 1998 and for the purposes of this article, ended in July 2002 (median follow-up 45 months). Recruitment and follow-up still continue. Participants were recruited through four sites: Memorial Sloan-Kettering Cancer Center in New York City, NY (426 women); M.D. Anderson Cancer Center in Houston, TX (86); Presbyterian Hospital in Dallas, TX (36); and the Wake Forest University Baptist Medical Center in Winston-Salem, NC (47). Patients from these centers were identified using tumor or surgical registries and patient or physician referrals. This study was approved by the institutional review board of each hospital as well as the US Department of Defense Human Subjects Committee.

Data Collection and Instruments

Demographics. Demographics included age, marital status, race/ethnicity, educational background, income, employment status, insurance status, household composition, and religious affiliation.

Medical and reproductive history. This included contraceptive use, births and incomplete pregnancies, pelvic surgery, and plans for future childbearing.

Personal habits questionnaire. Questionnaire included smoking and alcohol use, current height and weight, weight change, and exercise habits.

Medical chart review. Extensive chart reviews were performed at the recruiting institution and included the date and technique of breast cancer diagnosis, tumor size, location, grade, hormone receptor status, number of nodes examined, number of positive lymph nodes, type of definitive cancer surgery, reconstructive surgery, and other surgeries (eg, oophorectomy). Chemotherapy information (ie, dates, drugs, and dosages in milligrams) was gathered from medical oncology office records. For those receiving radiation, dose per treatment, treatment area, total dosage, and duration of treatment were recorded. Hormonal therapies, such as tamoxifen, were recorded with dates, routes of administration, and dosages.

Monthly bleeding calendars. Bleeding calendars were completed each month beginning on the date of recruitment. Participants marked on each day whether they experienced any menstrual bleeding and, if yes, if it was mild, moderate, or heavy. No hormone levels, such as follicle-stimulating hormone or estradiol levels, were collected.

Follow-up questionnaires. At baseline and every 6 months, patients completed quality-of-life questionnaires and health status updates, including cancer recurrences, reproductive events, surgical procedures or conditions that could change monthly bleeding status (eg, hysterectomy), and current or newly initiated drugs, including tamoxifen or other hormonal treatments, with dose, route, and dates of administration recorded. All follow-up data collection was conducted by mail through the study coordinating center at the Wake Forest University School of Medicine (Winston-Salem, NC).

Statistical Methods

All bleeding calendars for each participant were concatenated together to create a single record of bleeding since diagnosis. Missing data codes were inserted into the bleeding record to denote missing diaries (eg, for the days

between diagnosis and study entry and for calendars that were not returned). Each participant's bleeding record was then divided into 30 day months starting at the date of interest for each analysis (eg, diagnosis, last date of chemotherapy, and so on). A woman was coded as having bled during a particular month if she recorded any mild, moderate, or heavy bleeding in that 30 day period. Months for which more than half the days were missing were excluded from all analyses. Since we are using bleeding as a surrogate for ovarian function, the women who became pregnant during follow-up were not considered to be amenorrheic but were considered to have menstrual bleeding during their pregnancy. This occurred in 49 women for a total of 64 pregnancies. Bleeding data were not used after a woman recurred or developed a new cancer, since these women routinely received additional treatments that would influence ovarian function.

The mean percentage of women who experienced bleeding was calculated across time within selected subsets of interest (eg, age groups and chemotherapy regimens). Splines were used to generate smoothed curves through these mean percentages. Logistic regression models were used to assess the effect of selected demographic, pathologic, and clinical characteristics on monthly bleeding. The generalized estimating equations method was used to account for the repeated (ie, monthly) records for each participant. The correlation within participants was modeled using an autoregressive covariance structure, assuming that responses closer in time are more highly correlated than those far apart in time. All covariates were fixed except for hormonal treatment, which was included as a lag1 time-varying covariate. Time was included in the model as a quadratic factor. Interactions between time and treatment were assessed.

RESULTS

Demographic and Clinical Characteristics

Six hundred twenty-seven women were accrued between January 1998 and July 2002. Of those, 595 returned one or more monthly bleeding calendars and are included in these analyses. Median age was 39.5 years (range, 20 to 45 years; Table 1). The majority of women were white (88%), married (75%), had children (63%), and were college graduates (66%).

Treatment and pathologic variables are summarized in Table 2. All women had breast surgery: 306 women (51%) had breast conservative surgery (all but nine with postoperative breast radiotherapy); 289 women had total mastectomy, of which 153 women had a lumpectomy first as an attempt at breast conservation. Of the 289 women with mastectomy, 171 women also underwent immediate reconstructive surgery and 122 of the 289 women received postmastectomy radiation therapy. Five hundred fifty-six women (94%) had a full axillary node dissection, and 26 women had a sentinel node biopsy only. On average, women had 14 nodes examined (range, 0 to 51) and 44% of the women had at least one positive node. The majority of tumors (65%) were ≤ 2 cm in diameter; 44% had cancer in their axillary lymph nodes; and 56% had both estrogen and progesterone positive receptors.

Daily Bleeding Records

On average, participants returned 92% of the bleeding records due while on study. Of the 595 women, the number of monthly calendars returned per participant was: > 60 months, 111 women; 49 to 60 months, 120 women; 37 to 48 months, 98 women; 25 to 36 months, 101 women; 13 to 24 months, 96 women; 1 to 12 months, 69 women. During the course of follow-up, 118 women stopped returning bleeding calendars but otherwise remained in the study for quality-of-life and medical history follow-ups. The majority of these women had an oophorectomy and/or hysterectomy (66 women), and

Table 1. Summary of Baseline Participant Characteristics (N = 595*)

Characteristic	No.	%
Clinic		
Memorial Sloan-Kettering (New York, NY)	426	72
M.D. Anderson (Houston, TX)	86	14
Wake Forest, (Winston-Salem, NC)	47	8
Presbyterian (Dallas, TX)	36	6
Age at diagnosis, years		
20-35	146	25
35-40	174	29
≥ 40	275	46
Age, years		
Median		39.5
Range		20-45
BMI†		
Underweight or normal, < 25	392	66
Overweight, 25-29.9	122	21
Obese, 30+	81	14
BMI		
Median	23.2	
Range	16.9-56.9	
Race/ethnicity		
White	526	88
African American	28	5
Hispanic	25	4
Asian/Pacific Islander	16	3
Marital status		
Single/separated/widowed	146	25
Married/marriage-like	449	75
Education		
< College graduate	204	34
College graduate/graduate school	390	66
Employment		
Unemployed/looking	16	3
Full-time homemaker	101	17
Full-time	325	55
Part-time	85	14
Disabled	37	6
Other	30	5
Gross household income, US $		
< $50,000 per year	168	29
$50,000-$100,000 per year	222	38
> $100,000 per year	194	33
Smoke 100 cigarettes		
No	338	57
Yes, former smoker	215	36
Yes, current smoker	42	7
Age at first menstrual period, years		
≤ 11	134	23
12	180	30
13	174	29
≥ 14	107	18
Full term births		
0	222	37
1	115	19
2	177	30
3+	81	14

Abbreviation: BMI, body mass index.
*Incomplete data for some characteristics.
†Centers for Disease Control (CDC) definitions.

Table 2. Summary of Local Treatment and Tumor Characteristics (N = 595*)

Characteristic	No.	%
Breast surgery		
Lumpectomy	306	51
Mastectomy with RT	122	21
Mastectomy without RT	167	28
Tumor size, cm		
≤ 2	372	65
2-5	169	30
> 5	28	5
Axillary surgery		
None	9	2
Sentinel biopsy only	26	4
Axillary dissection	355	60
Sentinel and axillary dissection	201	34
Nodes examined		
0	10	2
1-10	193	33
11-20	247	42
> 20	144	24
Nodes positive		
0	334	56
1-3	163	27
4-9	58	10
10+	40	7
Histologic grade		
I	42	9
II	161	34
III	269	57
Nuclear grade		
I	33	7
II	185	39
III	256	54
Estrogen/progesterone status		
−/−	176	30
−/+	24	4
+/−	55	10
+/+	323	56

Abbreviation: RT, radiotherapy.
*Incomplete data for some characteristics.

follow-up because of death (40), lost to follow-up (53), and other reasons (83), including recurrences and lack of time or interest.

Adjuvant Therapy

Most women (523 of 595; 87%) received chemotherapy, mainly postoperatively; although, 65 of the 523 women (12%) received preoperative chemotherapy. The most common chemotherapy drugs received were cyclophosphamide (C; n = 507), doxorubicin (Adriamycin; Pharmacia, Milan, Italy [A]; n = 426), paclitaxel (Taxol, Bristol-Myers Squibb, New York, NY [T]; n = 230), fluorouracil (F; n = 178), methotrexate (M; n = 96), and docetaxel (Taxotere; Aventis Pharma Ltd, Dagenham, UK [D]; n = 50). Twenty-four women received other chemotherapy drugs, but no single drug was given to more than 10 individuals. The most common regimens were AC (n = 120), ACT (n = 168), CMF (n = 83), FAC (n = 38), FACT (n = 34), and ACD (n = 19). The median duration of adjuvant chemotherapy was 190 days.

The median, 10th, and 90th percentiles for number of doses, total dose, and mg per m^2 are presented in Table 3. Most of the regimens

40 women reported amenorrhea of greater than 24 consecutive months and were allowed to discontinue their calendars unless bleeding resumed, which did not occur in any of these participants. One hundred sixty-six women stopped the study completely during

Table 3. Dose Information by Regimen: Median and Range (10th-90th Percentiles)

Regimen	Doxorubicin		Cyclophosphamide		Paclitaxel		Docetaxel		Fluorouracil		Methotrexate	
	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range
AC, n = 120												
No. doses	4	4-4	4	4-4								
Total dose	400	350-458	4,000	3,400-4,560								
Mg per m²	60	56-62	598	561-617								
ACT, n = 168												
No. doses	4	4-4	4	4-4	4	4-4						
Total dose	408	360-468	4,080	3,600-4,800	1,173	972-1,372						
Mg per m²	60	57-63	596	570-626	174	163-183						
ACD, n = 19												
No. doses	4	4-6	4	4-6			4	1-12				
Total dose	424	270-656	4,200	2,416-6,516			608	200-984				
Mg per m²	60	35-62	595	347-619			95	28-103				
FAC, n = 38												
No. doses	6	4-6	6	4-6					12	6-12		
Total dose	504	378-642	5,040	3,900-6,420					9,000	4,675-12,420		
Mg per m²	49	42-54	495	472-559					500	487-576		
FACT, n = 34												
No. doses	4	4-5	4	4-5	4	4-4			8	3-8		
Total dose	360	300-500	3,550	2,808-4,400	1,332	1,040-1,800			6,400	2,200-8,000		
Mg per m²	50	49-59	502	487-576	183	153-247			499	487-576		
CMF, n = 83												
No. doses			8	6-56					8	6-12	8	6-12
Total dose			7,920	5,400-1,2600					7,906	5,200-11,800	528	418-792
Mg per m²			595	100-620					596	514-619	40	38-42

Abbreviations: AC, doxorubicin, cyclophosphamide; ACT, doxorubicin, cyclophosphamide, paclitaxel; ACD, doxorubicin, cyclophosphamide, docetaxel; FAC, fluorouracil, doxorubicin, cyclophosphamide; FACT, fluorouracil, doxorubicin, cyclophosphamide, paclitaxel; CMF, cyclophosphamide, methotrexate, fluorouracil.

were internally consistent, meaning that women on the same regimen received similar doses and cycles. No patients were treated with dose-dense regimens. Women who were treated with AC, either alone or in combination with T or D, received approximately 4,000 mg of C in four cycles and 400 mg of A in four cycles. In the ACD regimen, the amount and frequency of D administration was quite variable and the dose and frequency for A and C had greater range than in the AC and ACT programs. Only 19 women were treated with ACD, but the data are included as it represents some of the first available information on ovarian toxicity with D in the adjuvant setting. In the FAC regimen, the median number of doses was six, and these women received larger total doses of A and C than those who received the standard regimen of four doses of AC alone. In the FACT regimen, the total median doses of A, C, and F were reduced compared with FAC. The typical schedule of CMF was approximately 600 mg/m² of C, 600 mg/m² of F, and 40 mg/m² of M, each given for eight cycles. Oral C constituted all or part of the C for 11 women. These doses are included in the intravenous C total. Hormonal therapy was given to 340 of the 595 women (57%); 329 of these women received tamoxifen. Of the 72 women who did not receive adjuvant chemotherapy, 31 women (43%) received tamoxifen and one woman received anastrozole.

Menstrual Cycle Maintenance

The proportion of women with monthly bleeding dropped dramatically as the study population started the first doses of adjuvant therapy (Fig 1). As chemotherapy ended, the percentage of the women with monthly bleeding began to increase over the following months. A high of almost 55% of women with monthly bleeding by 15 months

after diagnosis was reached, after which the proportion gradually declined to 35% experiencing monthly bleeding 5 years after diagnosis.

Figure 2 shows the proportion of women with monthly bleeding after the completion of chemotherapy, according to age at diagnosis. The date therapy was completed is used as the beginning time point in this and subsequent figures. Women of all ages experienced disruptions in their menstrual function. However, a greater proportion of women age 40 or older had no menstrual bleeding at the end of chemotherapy and no recovery of bleeding in the follow-up years compared with younger women. Menstrual cycling recovered rapidly for those younger than 35 years, with the proportion with bleeding rising to approximately 85% at 6 months following the end of chemotherapy and remaining relatively constant. The recovery was less pronounced for women between the ages of 35 and 40, with a peak of 61% experiencing monthly bleeding 6 months following the end of chemotherapy to a low of 45% with bleeding at 5 years.

Figure 3 shows the proportion of women with monthly bleeding after the completion of chemotherapy, according to chemotherapy regimen. For reference, we have also included the group of women (N = 72) who did not receive chemotherapy (median age, 41 years; range, 25 to 45 years of age). The beginning point for these women is offset by 190 days, which is the median time to the completion of chemotherapy. Treatment with AC alone resulted in a dramatic decrease in the proportion with monthly bleeding. This was followed by several months of a gradually increasing rate of menstrual bleeding, and then a rather steady plateau of a similar proportion of women with monthly bleeding for the remainder of the study period. T added to the AC
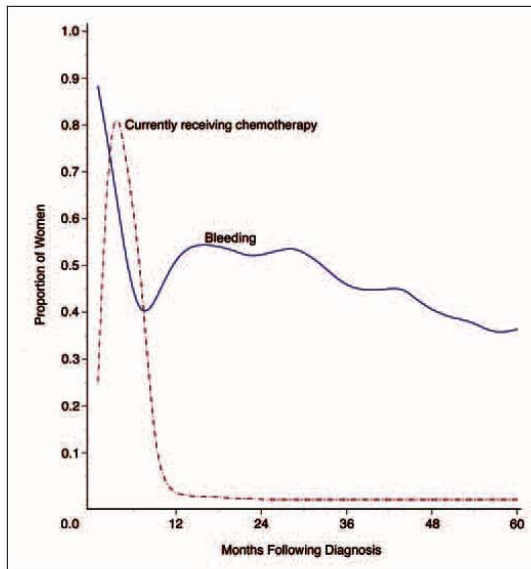
Fig 1. Menstrual bleeding after cancer diagnosis and chemotherapy (n = 595).

Fig 3. Bleeding after chemotherapy by type of regimen. AC, doxorubicin and cyclophosphamide; ACT, doxorubicin, cyclophosphamide, paclitaxel; CMF, cyclophosphamide, methotrexate, fluorouracil; ACD, doxorubicin, cyclophosphamide, docetaxel.

program led to a small further decline in the proportion with bleeding that was maintained over the course of the study, with a curve somewhat parallel to that of AC alone. D added to AC decreased the proportion with monthly bleeding even more than the addition of T, but, by 3 years, the ACT and ACD patients had similar monthly
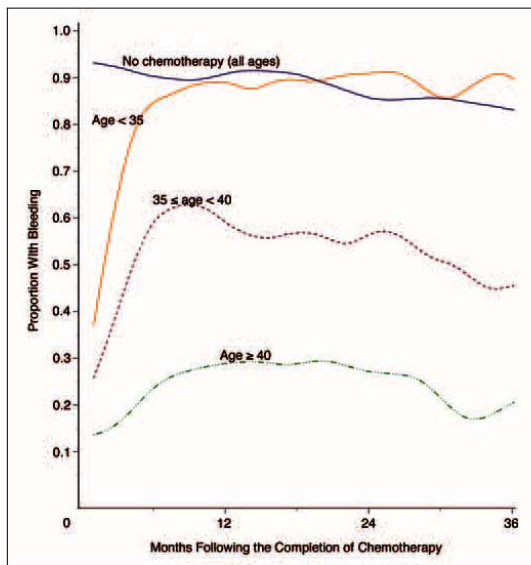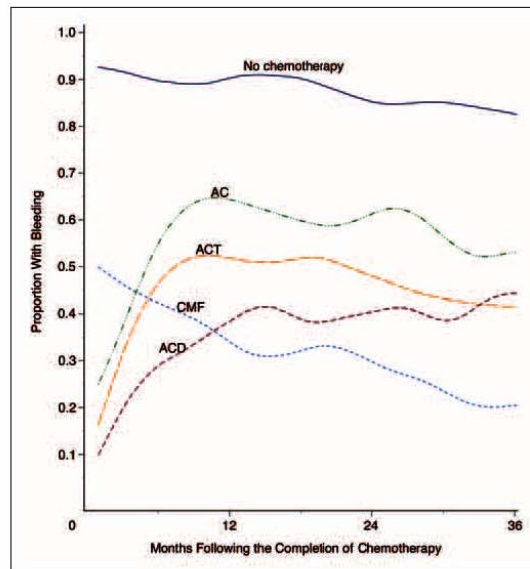

Fig 2. Bleeding after chemotherapy by patient age.

bleeding. A much different effect of CMF on ovarian function was noted. CMF resulted in a greater percentage of women who continued monthly bleeding in the initial months after treatment, but this initial percentage did not increase as there was no recovery phase, and in the follow-up years, there was a steadily diminishing proportion of women with menstrual bleeding.

A multivariable logistic model incorporating the variables presented in Tables 1 and 2 was completed to simultaneously examine the major clinical and demographic determinants of menstrual bleeding. Age ($P < .01$) and nodes positive ($P < .01$) were significantly associated with bleeding. The odds of bleeding decreased by 24% for each additional year of age and decreased by 11% for each additional positive node. Multivariable analyses confirmed the descriptive results that women receiving CMF were more likely to bleed during the first month following chemotherapy than women on any AC containing regimens (CMF v AC: odds ratio [OR] = 2.9; 95% CI, 1.7 to 5.0), but, by 1 year and thereafter, these women were less likely to bleed than those who received the AC regimens (except for ACD; CMF v AC at 2 years: OR = 0.27; 95% CI, 0.16 to 0.47). Women receiving tamoxifen were less likely to have monthly bleeding by 1 year following chemotherapy (OR = 0.50; 95% CI, 0.37 to 0.67). This effect became nonsignificant by 3 years.

DISCUSSION

This study reaffirmed that older age is strongly related to decreased menstrual bleeding. Age has been acknowledged as a factor in chemotherapy-related premature menopause, as in natural menopause. Younger women require more chemotherapy to develop

gonadal failure,[7] which probably relates to the smaller number of existing oocytes in older women.[16,17] Approximately 25% of American women age 44 to 49 years will experience menopause.[18] This age-related entrance into menopause probably accounts for why study subjects with no chemotherapy became amenorrheic during the follow-up period. Similar findings were reported in an untreated group of older premenopausal women in a recent randomized trial.[19]

A major finding of this study is that the proportion of women at any age with menstrual cycling varied depending on which chemotherapy regimen was used and the number of months since treatment completion. Goldhirsch et al[10] found that one perioperative dose of CMF was associated with a 10% incidence of menopause; rates increased to 33% and 61% after 6 and 12 months of CMF, respectively. Previous studies have established the efficacy of intravenous CMF as adjuvant therapy for breast cancer,[20,21] which was the primary mode of CMF administration in this study. Similar to our findings, a study of CMF, including both intravenous and oral regimens, as compared with goserelin, showed lower rates of amenorrhea in the CMF group at 6 months (59% v 95%), but greater rates of amenorrhea at 3 years (88% v 23%, respectively).[22] Amenorrhea seems most related to the cumulative dosage of C, and probably because of a lower total dose of C, almost all programs based on anthracyclines have less premature ovarian failure,[7,8] with one recent exception.[23] Much less is known about other combinations. The effect of the newest agents, T and D, has been assessed in several studies.[24-26] In one recent report, amenorrhea was present in 61.7% of those receiving D, A, and C versus 52.4% with FAC.[25]

In the present study, tamoxifen accounted for a modest, but significant decrease ($\approx$15%) in menstrual cycling at 1 and 2 years,

regardless of the chemotherapy program. Premenopausal women generally continue to menstruate while on tamoxifen although menses can become irregular.[27,28] The effect on the ovary is assumed to be reversible and temporary.

Limitations of the current study include a highly educated study population, only 12% minorities, and women recruited primarily from the eastern and southern United States. The menstrual bleeding status of those who stopped the study is unknown and the reasons for dropping out are assumed to be unrelated to the menstrual bleeding. Other limitations include the lack of classifying ovarian function with blood or urinary hormone assays. There are, however, no clinical parameters for defining chemotherapy-related amenorrhea.[29] Hormone assays could have been confusing because estradiol may remain high after chemotherapy-related amenorrhea.[30] Even with age-related (natural) perimenopause and menopause, direct assessment of menopausal status is often difficult.[31] Early follicular phase assays of follicle-stimulating hormone, estradiol and inhibin B, may predict ovarian reserve, although, these assays have been used, thus far, only in age-related assessments of women seeking assisted reproduction.[32,33]

These results provide important contributions regarding menstrual cycling following chemotherapy. For women concerned about the effects of premature menopause, including infertility, it is key to consider their age when considering treatment options. These results can facilitate decision making by women and their physicians who are attempting to balance the risk of breast cancer recurrence with the risk of ovarian failure and the desire to maintain menstrual cycling and/or fertility.

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Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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